American Journal of Obstetrics and Gynecology

VOL. 44 DECEMBER, 1942 NO. 6

American Gynecological Society

Sixty-Seventh Annual Meeting, June 15 to 17, 1942

(Concluded)

MALIGNANCY SUBSEQUENT TO IRRADIATION OF THE UTERUS FOR BENIGN CONDITIONS*

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PUBLISHED references to the occurrence of uterine malignancy at varying intervals after irradiation for supposedly benign conditions have appeared from time to time during the past two decades. The total of reported cases is relatively small, most of them having been mentioned in follow-up studies relating to the employment of radium and x-ray for the control of benign uterine hemorrhage.

Macfarlane,[8] in 1932, reviewed the literature subsequent to 1915, and briefly analyzed 29 reported cases, all from German sources, adding one of her own. In addition she quoted the findings of Werner, of Vienna, and Vogt, of Tübingen, whose combined figures revealed an incidence of 0.35 per cent of uterine malignancy subsequent to the irradiation treatment of 3,980 patients for fibromyomas or climacteric bleeding. Since then mention of similar cases has appeared in articles by H. C. Taylor, Jr.,[16] Corscaden,[2] Schmitz,[14] Norris and Behney,[9] Strachan,[15] Luker[7] and Costolow.[3] Occasionally similar occurrences were spoken of in the appended discussions of others. All in all, 71 cases have come to our attention in this way, but we admit that other

*Presented at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

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references may have been overlooked. The site of the malignancy was cervical in 18, fundal in 40, and not mentioned in 13.

To this total, we now add 20 additional cases, with accompanying data and appropriate comment. The first group comprises 7 patients with cervical carcinoma and the second includes 12 patients with fundal carcinoma and one with myosarcoma.

To justify a contribution such as this, it is necessary to furnish factual evidence of practical value and to determine whether or not certain factors influence the subject at issue. This cannot be done by creating hypotheses, but only by a critical evaluation of the evidence presented in each particular case.

Certain pertinent questions naturally arise at the outset of this investigation. They may be summarized to some extent as follows:

1. What type of benign lesions were subjected to irradiation therapy and what other procedures accompanied it?
2. Was an irradiation menopause produced?
3. What time intervened between the treatment for the benign condition and the discovery of malignancy?
4. In what location was the subsequent malignancy found, what was the extent of the lesion, what did the histopathology reveal, and was the grade of malignancy of any particular significance with respect to the final outcome?
5. Might malignancy have been present at the time of the primary treatment and overlooked because of errors of omission?
6. Was there any reason to believe that the irradiation therapy either retarded or accelerated the development of uterine malignancy?
7. What ways, if any, may be found to avoid a repetition of these occurrences?

Detailed analyses of the two series are first presented, followed by our own conclusions and subsequent comment with respect to the experience of others.

I. PATIENTS WITH CERVICAL CARCINOMA PREVIOUSLY TREATED WITH IRRADIATION FOR A SUPPOSEDLY BENIGN CONDITION

Of 481 patients with cervical carcinoma seen on the gynecologic ward service at Jefferson Medical College Hospital between 1921 and 1942, there were 7 who had received irradiation therapy for an apparently benign condition, from two to eleven years prior to the diagnosis of malignancy.

Microscopic and pathologic reports relating either to cervical or endometrial tissue or both, secured at the time of the primary treatment, were available for study, and have been reviewed in the light of subsequent developments. Brief analyses of each history, limited to pertinent facts and with appropriate comment, are appended, the patients being considered in the chronologic order in which each came to our attention. The term "menopause" is used in a restricted sense, referring merely to the cessation of uterine bleeding. Clinical grouping of the cervical carcinoma follows the Schmitz classification.

CASE 1.—S. B., aged 44 years, multipara, was admitted Jan. 24, 1933. Diagnosis: squamous cell carcinoma of cervix (Group III, low grade malignancy), with uterine myomas. No establishment of menopause. History of continuous discharge for one year; menses irregular since previous irradiation nine years before. Radium therapy (3,600 mg. hr.) followed by external irradiation (1,760 r. to each of 4 portals) was of no avail, and patient died one year later.

Previous Treatment.—On Nov. 12, 1924, because of metromenorrhagia and pelvic relaxation, curettage and posterior colporrhaphy were performed, together with an intrauterine application of 1,200 mg. hr. of radium for interstitial myomas. Cervix reported to be bilaterally lacerated and everted, but not biopsied or treated. Histologic report on curettage was "hyperplasia of the endometrium, suspicious of malignancy."

Comment.—The review of this section is informative, since it reveals a late interval endometrium, with no suggestion of malignancy. Of decidedly more interest was the discovery of a small piece of cervical tissue, evidently curetted from the portio, which shows in one location an ill-defined basement membrane with some epithelial elements infiltrating the stroma and evidencing mitotic activity and polychromatosis. Unfortunately the tissue is too minute for satisfactory diagnosis. In retrospect, criticism is tenable from several angles. First, the use of radium in a patient of 35 for the treatment of interstitial myomas, entirely apart from its failure to control adequately the growth of the neoplasm; second, the failure to biopsy and to treat properly the abnormal cervix primarily; third, the incorrect interpretation of the curettings, excusable to some extent because of the changing concepts that have evolved since then with respect to the histology of the endometrium.

CASE 2.—L. G., aged 42 years, multipara. Was admitted June 21, 1934. Diagnosis: squamous cell carcinoma of cervix (Group II, intermediate grade of malignancy) with uterine myomas. There was no establishment of the menopause. A history of menorrhagia beginning two years before was given. She was treated with external irradiation. Pronounced bleeding finally resulted in further examination, positive cervical biopsy, and application of radium therapy (4,200 mg. hr.) with subsequent external irradiation (1,600 r. to each of 4 portals). Treatment was of no avail and patient died seven months later.

Previous Treatment.—The patient was first seen in the Out-Patient Department on June 10, 1932, because of menorrhagia; pregnancy was excluded, and a diagnosis of myoma uteri made. Condition of cervix was not noted. Diagnostic curettage was not performed and external irradiation was instituted (1,800 r. to each of 4 portals). "Spotting" occurred subsequently at varying intervals and the patient was reexamined on five occasions during that time, but it was not until two years had elapsed that a profuse hemorrhage finally indicated cervical inspection and biopsy.

Comment.—Severe criticism is justifiable. First, primary inspection and careful study of the cervix were neglected; second, faulty judgment was exhibited in employing external irradiation without preliminary curettage.

CASE 3.—M. M., 49, multipara, was admitted July 29, 1934. Diagnosis: squamous cell carcinoma of cervix (Group III, intermediate grade of

malignancy). Irradiation menopause six years before. History of vaginal bleeding and discharge for nearly two months prior to admission. Radium (3,600 mg. hr. and 1,500 mg. hr.) on two occasions. Death occurred one year later.

Previous Treatment.—On July 23, 1928, because of menorrhagia of one year's duration, a cervical polyp was removed followed by curettage and an intrauterine application of 1,200 mg. hr. of radium for small interstitial and subperitoneal myomas. A bilaterally lacerated cervix was neither biopsied nor treated. The curettings and polyp were reported to be benign.

Comment.—A review of the sections indicates an interval endometrium with a local hyperplasia in one area. The polyp, too, may be regarded as benign, although in one location near the surface the cells resemble epithelium, and show polynucleosis and mitotic activity, the significance of which is questionable. The most pointed criticism in the early management of this case is that cervical biopsy and treatment, either with cautery or surgery, might well have had an immediate and curative effect. It is unlikely that the presence of the previously removed polyp had any bearing on the final outcome.

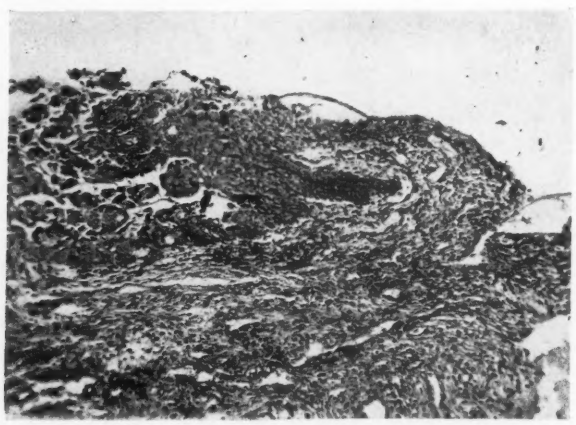


Fig. 1.—Case 4 (cervical group). Area suspicious of early malignant change in cervical biopsy. (Photomicrograph ×100.)

CASE 4.—E. D., aged 56 years, multipara, was admitted July 9, 1936. Diagnosis: squamous cell carcinoma of cervix (Group II, low grade malignancy). Irradiation menopause occurred four years previously. There was a history of bloody discharge of two weeks' duration, prior to admission. Radium therapy (3,600 mg. hr.) was given followed by subsequent external irradiation on two occasions, five months apart (1,870 r. and 1,680 r. to each of 4 ports, respectively), with survival for four years and eight months. Death was due to carcinoma.

Previous Treatment.—On April 21, 1932, because of menorrhagia of three months' duration and premenstrual "spotting" of one year's duration, curettage, biopsy, cauterization, and an application of 600 mg. hr. of radium to the uterine cavity for myomas were employed. In addition, a cystocele, rectocele, and an hypertrophied cervix were present. Adnexa were negative. Rapid report on the curettings and cervical tissue was requested, and this revealed an atrophic endometrium. While the biopsy sections from the cervix showed an intact

basement membrane in some areas, certain others showed several islands of epithelial cells beneath it. Of these, some were well differentiated, normally appearing cells of the squamous variety; in other areas, indicating an erosion, the cells were of different sizes, showing mitosis and polynucleosis. The conclusion stated was that although the evidence was insufficient to justify a diagnosis of malignancy at the site of the erosion, nevertheless the lesion was sufficiently suspicious of early malignant change to justify a careful follow-up (Fig. 1).

Comment.—In this instance a golden opportunity for prophylaxis was lost, due to the indifference of the patient on the one hand and to the lack of an aggressive follow-up on the other.

CASE 5.—C. C., aged 60 years, multipara, was admitted Sept. 7, 1937. Diagnosis: squamous cell carcinoma of cervix (Group III, high grade malignancy). Irradiation menopause occurred ten years before. There was a history of vaginal bleeding for six months prior to admission. External irradiation (1,870 r. to each of 4 ports) was followed by radium therapy (3,600 mg. hr.), and a further course of external irradiation (1,300 r. to each of 4 ports, and 1,100 r. to perineum). The patient survived but one year and four months.

Previous Treatment.—On May 17, 1926, at the University of Pennsylvania Hospital, curettage, vaginal myomectomy and an application of 1,200 mg. hr. of radium to the uterine cavity were carried out together with hemorrhoidectomy, because of myoma uteri, pedunculated cervical myoma and hemorrhoids. There was no biopsy or treatment of cervix. Dr. Sidney Dunne reviewed the sections and established a diagnosis of normal proliferative endometrium. However, no mention was made of the condition of the cervix, and apparently there was no biopsy; neither was the cervical myoma reported histologically.

Comment.—It is unlikely that malignancy was present in the cervix or in the cervical myoma at the time of the first operation, for no further symptoms of consequence appeared until nearly eleven years had elapsed.

CASE 6.—C. T., aged 61 years, multipara, was admitted Aug. 29, 1938. Diagnosis: squamous cell carcinoma of the cervix (Group III, low grade malignancy). Irradiation menopause occurred nine years previously. A history of vaginal bleeding for three months before admission was given, followed by "spotting" and pain in lower right quadrant. Radium therapy (3,600 mg. hr.) followed by external irradiation (2,700 r. to each of 4 ports) was given. Patient has now survived without evidence of recurrence for nearly four years.

Previous Treatment.—Left oophorectomy was performed in 1903. On Jan. 24, 1929, because of menorrhagia of two years' duration, curettage, and an intrauterine application of radium (600 mg. hr.) were performed for fibrosis uteri. The cervix was reported to be lacerated, the uterus of normal size and position, and the adnexa were negative. There was no biopsy or treatment of cervix. Histologic report of the curettage reported the endometrial tissue to be hyperplastic in some areas and atrophic in others; also there was slight round cell infiltration and fibrosis of the endometrium in places.

Comment.—Review of the sections showed an interval type of endometrium, and no evidence of malignant change. No cervical tissue was available for study.

CASE 7.—M. W., aged 52 years, multipara, was admitted June 13, 1941. Diagnosis: squamous cell carcinoma of the cervix (Group I, low grade malignancy). Irradiation menopause occurred six years before with intermittent bleeding during the subsequent years. There was a history of irregular vaginal bleeding of three months' duration prior to admission. On June 16, 1941, diagnostic curettage was performed. The cervix appeared to be intact; the fundus was small and freely movable. Adnexa were negative. Curettage revealed a few normal endocervical glands, presenting atrophic changes, surrounded by a poorly vascularized dense stroma, most of the tissue being replaced by islands of tumor cells of the squamous variety, well differentiated, but presenting mitotic activity and polychromatosis. It was thought that the malignant growth had its origin in the endocervix and a second curettage with cervical biopsy was requested. Five days later, on June 21, the cervical canal was dilated and thoroughly exposed for curettage of the uterine cavity and adequate biopsy. This curettage showed an interesting picture: hyperplasia of the endometrium, and side by side with it a hyalinized, degenerated, and infiltrated tissue, having no resemblance to the endometrium. There was a diffuse infiltration of tumor cells with a tendency to island and strand formation, evidencing squamous characteristics and presenting mitotic activity and polychromatosis, a well-differentiated squamous cell carcinoma of the endocervix. Biopsies from the portio showed a benign cervical erosion with hyalin changes of the cervical wall, normal squamous epithelium with an intact basement membrane. External irradiation (2,700 r. to each of four portals) was employed prior to radium therapy (4,800 mg. hr.). Patient is apparently well after one year.

Previous Treatment.—Because of menorrhagia and metrorrhagia of a year's duration, together with perineal relaxation, diagnostic curettage, posterior colporrhaphy, and an intrauterine application of radium (1,200 mg. hr.) for fibrosis uteri were performed on June 10, 1935. A rectocele was present, the cervix was intact, and the fundus was relatively normal in size, position, and mobility. Adnexa were negative. There was no biopsy or treatment of the cervix. Histologically, the curettings revealed only a few tiny shreds, made up of an edematous stroma in which a few fragmented glands appeared, inadequate for satisfactory diagnosis.

Comment.—There is little to criticize in the early management of this patient. The intact cervix did not indicate biopsy; the curettage was negative.

SUMMARY AND CONCLUSIONS RELATIVE TO THE CERVIX GROUP

1. All the patients were multiparas, ranging in age from 42 to 61. Radium was used to treat fibromyomas in four and x-ray in a fifth. Two were treated with radium because of fibrosis uteri, or so-called functional bleeding. A plastic, polypectomy, and vaginal myomectomy were accompanying procedures in three patients, respectively. Biopsy with cauterization was done in but one case.

2. An irradiation menopause was produced in 5 patients ranging in age from 43 to 52 years at the time of treatment. None was produced in two patients, aged 35 and 40, respectively.

3. The time intervening between the benign treatment and the discovery of malignancy was 2, 4, 6, 6, 9, 9, and 11 years, respectively.

4. Squamous cell carcinoma developed in every patient. Clinically, one was in Group 1, two in Group 2, and four in Group 3 (Schmitz). This is a larger proportion of relatively early cases than has been our experience with the entire series of cervical carcinoma patients. Low grade malignancy was present in 4, intermediate in 2, and high in 1. No conclusion can be drawn from this, but it can be stated that the single picture of high grade malignancy was present in the patient who developed carcinoma eleven years after initial irradiation, the longest interval noted in the series. Of 4 patients who died within one and one-half years of treatment, only 1 exhibited a low grade lesion, while of 3 other patients with low grade lesions, 1 survived for nearly five years and 2 have remained well from one to four years.

5. There is no evidence to support a statement regarding the presence or absence of malignancy at the time of the initial irradiation, with the possible exception of the one patient in whom biopsy was performed (Case 4). In this particular instance the pathologist regarded the lesion with suspicion, and even though the cervix had been cauterized, the warning should have been heeded and subsequent hysterectomy performed. With three other patients (Cases 1, 3, and 6) recorded cervical lesions should have been biopsied and treated at the time of the primary irradiation. In two additional instances (Cases 2 and 5), no note of the condition of the cervix appears, and one of these patients received x-ray therapy for fibromyomas without cervical inspection or diagnostic curettage. In the seventh patient of the series, the cervix was described as intact when first seen (Case 7).

Errors of omission may be charged to the management of 6 of these patients when they were first seen. Interest was primarily centered on the fundal lesion. Endometrial curettage was properly employed and malignancy of the fundus excluded in all instances except the one in which x-ray therapy was used. In only 2 patients, however, was the cervix thought of in terms of potential malignancy, and in one of these (Case 4) the opportunity for prophylactic treatment was missed. In the other (Case 7) biopsy of the cervical canal beyond the intact portio followed promptly when evidence of squamous cell carcinoma presented in the curettage.

6. There is no substantial evidence to show that irradiation therapy of the uterine fundus either retarded or accelerated the development of the cervical malignancy in these patients.

7. The outstanding lesson that we have learned from this phase of the investigation, and the point that we think should be emphasized to others is this: Whenever diagnostic curettage is indicated, the procedure might well be accompanied with cervical biopsy as a matter of record, but especially if any abnormality is apparent. The area of biopsy

should include not only the portio and everted mucosa, but the lower cervical canal. The procedure ought not only to be applied to the suspected case of endometrial carcinoma but should be utilized whenever irradiation therapy is chosen for the treatment of either fibromyomas, fibrosis uteri, or functional bleeding. Eradication of any cervical pathology is equally essential.

II. PATIENTS WITH FUNDAL CARCINOMA AND ONE WITH SARCOMA PREVIOUSLY TREATED WITH IRRADIATION FOR A SUPPOSEDLY BENIGN CONDITION

Of 124 patients with fundal carcinoma seen on both the gynecologic ward and private services during the period previously mentioned, there were 12 who had received irradiation therapy for supposedly benign lesions, from two to twenty-three years prior to the frank diagnosis of malignancy. An additional patient similarly treated ten years before subsequently developed uterine sarcoma.

Complete studies are not available in four instances, because the records of the primary treatment are either faulty or inaccessible; the remaining 9 histories are complete in all details.

A. PATIENTS WITH INCOMPLETE RECORDS

CASE 1.—(Ward.) L. W., aged 61 years, nullipara, was admitted Dec. 11, 1924. Diagnosis: fundal carcinoma of advanced degree. Menopause occurred at the age of 51. A history of irregular vaginal bleeding of three years' duration four years after the menopause was given. At that time (1921) 1,200 mg. hr. of radium was administered at the Methodist Hospital, Philadelphia, with no report of curettage or histologic study. In 1923 the patient again received an intrauterine radium treatment for bleeding at the Lankenau Hospital, Philadelphia, at which time cancer of the uterus was said to have been diagnosed. A year later, following admission to Jefferson Hospital because of continued bleeding, curettage was performed. The vagina was atrophic, the cervix obliterated and the fundus enlarged. Sections were diagnosed as adenocarcinoma of the uterus. On Jan. 28, 1925, abdominal section revealed inoperable carcinoma of the uterus with bilateral involvement of the ovaries and metastasis to the omentum, sections of which showed adenocarcinoma, high grade malignancy. Death occurred within a few months (1925).

Comment.—Review of the sections of the curettage show little more than a diffuse picture of carcinoma, difficult to classify; those of the ovaries and omentum appear to be an adenocarcinoma with markedly anaplastic areas. Dr. Stanley Reimann, of the Lankenau Hospital, has also reviewed the curettage secured in 1923 and says that a diagnosis of carcinoma was not made at the time of the second radium application. In retrospect it would seem that this patient suffered from malignancy, most probably of the fundus, when she was first seen in 1921. Curettage and adequate treatment might have contributed to a more fortunate outcome.

CASE 2.—(Dr. Anspach.) B. G., aged 53 years, multipara, was admitted July 21, 1927. Diagnosis: fundal carcinoma, apparently limited to the uterus. Menopause occurred at the age of 42. Recurrent episodes of bleeding for three years prior to admission, beginning eight years after the establishment of the menopause. In 1924 a curettage and an application of radium for thirty-six hours was said to have been made to the uterine cavity. No verification of where or by whom this was done had been secured, but because of this history, on Aug. 2, 1927, complete abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. Enlarged lymph nodes were present in the omentum, and the uterine cavity contained an ulcerative, fungating mass that invaded the uterine wall. The adnexa were grossly normal. Histologically the tissue showed an adenocarcinoma of high grade malignancy (Grade IV). There was no demonstrable involvement of the adnexa. The patient survived the operation, but died one year later with spinal metastases.

Comment.—This patient very probably had carcinoma of the fundus from the onset of her postmenopausal bleeding three years before.

CASE 3.—(Dr. Anspach.) M. N., aged 52 years, nullipara, was admitted Nov. 23, 1929. Diagnosis: fundal carcinoma, apparently limited to the uterus. Menopause occurred at 40 years of age, evidently the result of radium treatment for myoma uteri, administered by the late Dr. John G. Clark at the Germantown Hospital, Philadelphia, in 1917. Six weeks prior to admission irregular vaginal bleeding had occurred, the first since the irradiation therapy twelve years before. Pelvic examination revealed an intact cervix, a mobile uterus of normal size and negative adnexa. Dr. Anspach tells me that he endeavored to secure data regarding Dr. Clark's original curettage, but a record could not be found at the Germantown Hospital; neither could Dr. Sidney Dunne find any record in the gynecologic laboratory at the University of Pennsylvania. On Nov. 26, 1929, curettage was performed and 2,400 mg. hr. of radium applied to the uterine cavity. Histologic report was adenocarcinoma of high grade malignancy (Grade IV). Sections were also submitted to Dr. C. C. Norris, who was reluctant to make a frank diagnosis of malignancy, but advised treating the lesion as carcinoma. On Jan. 21, 1930, complete abdominal hysterectomy and right salpingo-oophorectomy were performed. The left adnexa was densely adherent and was not removed. Multiple small myomas were present in the uterus, the endometrial cavity of which was entirely necrotic. Beneath this rather shallow area there was rather extensive infiltration of the musculature by masses of epithelium which in some places involved the entire thickness of the uterine wall. This tissue was undifferentiated and formed small solid masses. The removed right tube was uninvolved, the right ovary harboring a simple cyst. Postoperative courses of x-ray therapy were employed, but pelvic recurrence and pulmonary metastasis resulted in the death of the patient three years later.

Comment.—It is unfortunate that nothing definite can be stated with regard to the initial curettage by Dr. Clark, but from our knowledge of his meticulous procedures, it may be assumed that there was no question of malignancy twelve years prior to its discovery by Dr. Anspach.

CASE 4.—(Dr. Scheffey.) L. M., aged 65 years, multipara, was admitted Jan. 31, 1942. Diagnosis: fundal carcinoma, fairly well ad-

vanced. Menopause occurred at the age of 50 years. A history of menorrhagia at intervals for two years prior to admission was given. Because of this, 2,500 mg. hr. of radium was employed in a private hospital in July, 1940. There was no regular follow-up by the physician then in charge. Bleeding never ceased entirely and in September, 1941, the patient returned to him for advice. He referred her to a radiologist who employed weekly x-ray treatments (2,300 r. anteriorly and 400 r. posteriorly to the pelvis over a period of four months). No improvement resulted, and the patient consulted me. The presumptive diagnosis was apparent. Inquiry regarding the previous treatment resulted in the negative information that the original curettage was "inconclusive" and that no sections were available for study. The general condition of the patient was poor. On Feb. 2, 1942, curettage revealed an extensive pyometra, the sections showing adenocarcinoma, intermediate grade malignancy (Grade III) with extensive necrosis and degeneration. After subsidence of fever, external irradiation was employed, solely through posterior portals (2,200 r.), because of extensive anterior abdominal wall changes resulting from the previous saturation technique. The immediate response was beneficial. On Apr. 15, 1942, curettage was repeated and intrauterine radium applied (4,575 mg. hr.). Symptomatically, the patient has improved but to date there has been little change in the pelvic findings—an enlarged uterus with moderate sensitivity. Postirradiation surgery seems unwise in this instance.

Comment.—Radium therapy, without effective curettage or adequate pathologic study, and without follow-up observation and subsequent treatment of value may well be responsible for the present status of the patient.

B. PATIENTS WITH COMPLETE RECORDS

CASE 5.—(Dr. J. M. Fisher, deceased.) M. H., aged 43 years, nullipara, was admitted May 31, 1929. Unqualified clinical diagnosis of fundal carcinoma. There was a history of menorrhagia for five months, after an amenorrhea of three years' duration (since 1926). There was no record of the pelvic findings. Complete abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Grossly there was an extensive inflammatory reaction and necrosis throughout the uterine tumor, but there was no evidence of adnexal metastases. A histologic diagnosis of adenocarcinoma, high grade malignancy (Grade IV) was made. Recovery from the operation was followed eventually by vaginal and abdominal metastases that were refractory to x-ray therapy and the patient died one and one-half years later.

Previous Treatment.—Through the courtesy of Dr. Sidney Dunne previous operative records and histologic reports have been reviewed by him. On Nov. 29, 1922, the late Dr. J. G. Clark performed a curettage, trachelectomy, excision of vaginal cyst, and an application of 150 mg. hr. of radium to uterine cavity because of discharge and irregular uterine bleeding. Histologically, chronic endocervicitis and typical hyperplasia of the Swiss cheese pattern was reported. Again, because of irregular bleeding, on May 31, 1923, a curettage was repeated and 400 mg. hr. of radium was administered. This time curettage still presented endometrial hyperplasia, but to a lesser degree than in the previous study. Menses were regular until 1926, when amenorrhea occurred and continued as noted until 1929, when the present illness began.

Comment.—In this instance a preceding hyperplasia was present. Review of the sections showed a mixed growth to be present: in one location there was small acini formation, though not very well differentiated. Side by side with this area were rather well-defined islands and strands of tumor cells of squamous variety. It is possible therefore that the sections represent both fundus and endocervix, or it might be regarded as an adenoacanthoma.

CASE 6.—(Ward.) R. R. 57, nullipara, was admitted Dec. 29, 1936. Diagnosis: pelvic tumor. History of an irradiation menopause existing for ten years, and discomfort in the lower left pelvis for three weeks. There was some vaginal discharge but no bleeding. Pelvic examination revealed a cystocele, rectocele, and cystic cervix; the fundus was irregularly enlarged to the size of an eight weeks' pregnancy, and there was also an enlargement in the right adnexal region that suggested a parovarian cyst. General condition was inferior. Because of the uterine enlargement, which suggested a myoma, and after an adequate period of observation, on Jan. 23, 1937, diagnostic curettage was performed and radium placed in the uterine cavity, pending a rapid report of the curettage. This proved to be malignant and a dosage of 3,000 mg. hr. was employed. The cervix was not biopsied, since it presented no eversion, and was not friable. Histologically the sections were reported as revealing a highly degenerated tissue, devoid of glandular elements, in the less degenerated portions of which the connective tissue stroma showed diffuse infiltration by epithelial cells, unequal in size and irregular in shape. Some areas presented small clumps of epithelial cells, but a diagnosis of high grade malignancy, solid adenocarcinoma of the fundus (Grade IV), seemed warranted. The therapy was ineffectual and the patient died in three months' time.

Previous Treatment.—Ten years before (1927), curettage followed by radium therapy (900 mg. hr.) had been performed at Hahnemann Hospital, Philadelphia, because of excessive vaginal bleeding. A marked fibrosis of the lower fundus and upper cervical canal was observed clinically together with a cervical erosion. No biopsy was done. Curettage was insufficient for diagnosis, but the patient remained under observation for two years (1929), and there was no further bleeding. For this information I am indebted to Dr. N. V. Ludwick, radiologist at Hahnemann Hospital. On Nov. 9, 1935, appendectomy was performed by Dr. K. E. Fry, on the general surgical service at Jefferson Hospital. Pathologically, acute suppurative appendicitis was reported. No pelvic examination was recorded on the occasion of this admission, and there was no note in the operative report of any pelvic pathology being observed at the time of the appendectomy.

Comment.—Principal interest in this case attaches to the peculiar character of the curettage. No errors of omission can be attributed to the clinical management. There seems to be no relationship between the primary treatment for fibrosis uteri and later developments. A pelvic examination at the time of the operation for acute appendicitis might have been revealing.

CASE 7.—(Dr. Scheffey.) B. C., aged 61 years, multipara, was admitted Dec. 16, 1938. Presumptive diagnosis: fundal carcinoma. Menopause occurred at 42 years of age (1919), followed soon afterward by vaginal bleeding, becoming excessive at 50 (1927), when myoma uteri

were diagnosed but not treated. Bleeding ceased for a year and then recurred slightly every five or six months over a period of four years until January, 1932, when curettage and radium therapy were employed. This caused cessation of bleeding for seven years when readmission was necessitated by the appearance of a pinkish discharge. Cervix was intact, and the fundus somewhat enlarged and irregular but freely movable. Adnexa were negative. On Dec. 17, 1938, curettage was performed and radium placed in the uterine cavity pending a rapid report on the curettings. This revealed an adenopapillary growth of low grade malignancy (Grade I), and a dosage of 4800 mg. hr. was employed. There have been no return of symptoms to date.

Previous Treatment.—At the time of the primary curettage and radium treatment (2,400 mg. hr.) on Jan. 8, 1932, the curettings were reported as revealing small areas of hyperplastic columnar epithelium with irregular acini in the superficial layers of the myometrium, the cells being hyperchromatic, varying in size and shape, with many of the small acini lined by numerous layers of epithelium instead of one. The diagnosis was summed up as follows: "The change in the epithelium of the endometrium is very suggestive of malignancy, but serial sections were cut from the tissue and many sections examined from various levels of the tissue, and no frank evidence of definite infiltration by the epithelium could be demonstrated."

Comment.—A review of the original sections lead us to believe that the lesion should have been regarded as a definite low grade malignancy (Grade I) from the first. Radical operation should have followed the irradiation therapy in due time. Surgery was contraindicated in 1938.

CASE 8.—(Ward.) B. S., aged 60 years, nullipara, was admitted Apr. 18, 1939. Presumptive diagnosis: fundal carcinoma. There was a history of vaginal bleeding of five months' duration, the first time after an irradiation menopause produced thirteen years before (1926). Cervix was intact, fundus normal in size and position, and adnexa negative. Curettage was performed on Apr. 22, 1939, and radium was placed in the uterine cavity pending a rapid report of the curettage. This was diagnosed adenocarcinoma, low grade malignancy (Grade II) (Fig. 3). A total dosage of 4,800 mg. hr. of radium was employed. There have been no further symptoms. On May 22, 1941, the cervix was dilated and the uterine cavity sounded. No bleeding was produced, but no curettage was performed. Patient was apparently well three years later.

Previous Treatment.—On Sept. 27, 1926, because of menorrhagia and metrorrhagia, curettage was followed by radium (1200 mg. hr.) which was employed to control functional bleeding. Pelvic examination was grossly negative. Sections from the curettings were reported as "polypoid endometritis" and no further treatment was advised (Fig. 2).

Comment.—Review of the original section in this case leads us to believe that the original diagnosis was a mistaken one. It is similar to the recent one, and should be regarded as an adenocarcinoma of low grade malignancy (Grade II). The astonishing feature of this case is the subsidence of clinical symptoms for a period of thirteen years after a relatively small irradiation dosage. In view of this fact, and because of the patient's advanced age (60), together with a certain degree of asthenia, it was thought advisable to depend upon the larger dosage of radium, and post-irradiation surgery was not advocated.

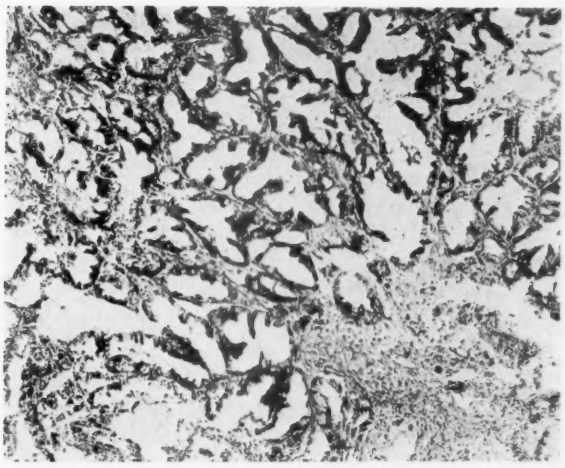


Fig. 2.—Case 8 (fundal group). Low grade malignancy (adenoma malignum, Grade II), reported thirteen years before as "polypoid endometritis." (Photomicrograph ×50.)

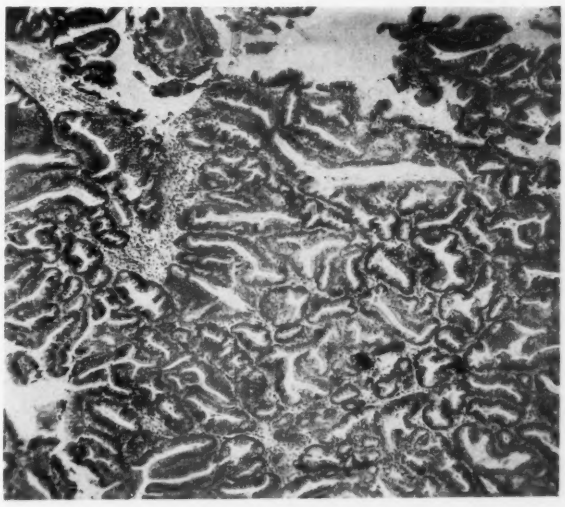


Fig. 3.—Case 8 (fundal group). Low grade malignancy (adenoma malignum, Grade II), when carcinoma was finally diagnosed. (Photomicrograph ×50.)

CASE 9.—(Dr. Scheffey.) M. S., aged 60 years, multipara, was admitted Mar. 26, 1940. Presumptive diagnosis: relatively advanced fundal carcinoma. Menopause occurred at 35 years of age. There was a history of intermittent vaginal bleeding of two years' duration, but of daily occurrence for three months prior to admission. Cervix was intact, slightly enlarged symmetrical uterus, and adnexa negative with exception of bilateral tenderness on deep palpation. On Apr. 1, 1940, curettage was done and radium placed in the uterine cavity pending a rapid report of the curettage. This revealed an adenocarcinoma of low grade malignancy (Grade II). Radium dosage of 5,400 mg. hr. was employed, and six weeks later, on May 16, 1940, complete abdominal

hysterectomy and bilateral salpingo-oophorectomy were performed. An interstitial myoma was observed in the anterior uterine wall. There was no gross evidence of extension or metastasis from the uterus. The mucosa was thickened in several areas of the uterine cavity, being friable and partially invasive of the myometrium at these places. The adnexa appeared atrophic. Sections revealed an adenocarcinoma of low grade malignancy, as did the previous diagnostic curettage. No metastatic lesions were observed in the tubes and ovaries. Convalescence was complicated by three distinct attacks of pulmonary emboli, but recovery was complete. There is no evidence of recurrence to date.

Previous Treatment.—During a period of eighteen months prior to admission, patient had been receiving external irradiation for the treatment of fibromyomas by a radiologist; this in view of the fact that the bleeding was definitely postmenopausal; neither had diagnostic curettage ever been performed.

Comment.—Further comment would be superfluous.

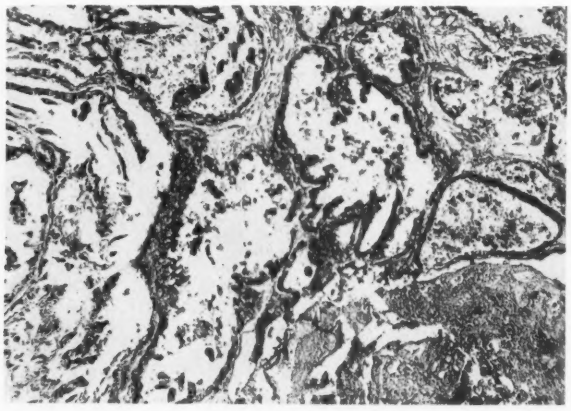


Fig. 4.—Case 10 (fundal group). Mucocellular adenocarcinoma, intermediate grade of malignancy (adenocarcinoma, Grade III). (Photomicrograph ×50.)

CASE 10.—(Ward.) E. H., aged 55 years, multipara, was admitted Jan. 15, 1941. Presumptive diagnosis: fundal carcinoma. There was a history of bloody vaginal discharge of six months' duration, the first since the initiation of an irradiation menopause with radium eleven years before (1930). Cervix was intact, slightly enlarged symmetrical fundus, and adnexa were negative. Curettage on Jan. 16, 1941, revealed an unusual histologic picture, viz., "arborescent tumor growths consisting of many incomplete acini and papillary formations, composed of large cells containing large nuclei surrounded by a great deal of cytoplasm, and resembling mucin cells." Diagnosis, mucocellular adenocarcinoma fundus uteri, and intermediate grade malignancy (Grade III) (Fig. 4). The curette distinguished a submucous tumor, and complete hysterectomy was deemed advisable after necessary attention to patient's general condition, since on a previous admission cerebrospinal syphilis had been diagnosed, although serology was now negative. On Feb. 12, 1941, complete abdominal hysterectomy and bilateral salpingo-oophorectomy was performed. Grossly, fibromyomas were present in the uterus in addition to the carcinomatous growth invading the myo-

metrium. The adnexa were grossly normal. Histologically the sections were similar in appearance to those secured at the time of the diagnostic curettage. Recovery from operation was uneventful and patient has remained well to date.

Previous Treatment.—In 1918, when patient was 32 years of age, a pelvic tumor was said to have been removed in the Chester, Pa., Hospital. This was not verified. On July 28, 1930, when patient was 44, polypectomy with curettage and an intrauterine application of radium (1,200 mg. hr.) were performed because of metromenorrhagia of two months' duration, supposedly due to the polyp and to uterine myomas. Surgery was discouraged at that time because the patient had positive serology (blood and spinal fluid), and cerebrospinal syphilis was thought to be present. Histologically the sections from the curettage revealed atrophic endometrial glands and marked fibrosis of the stroma with beginning calcific formation. The cervical polyp presented an erosion, both cylindric and squamous epithelium, but was benign.

Comment.—No relationship seems probable between the histologic studies made at an interval period of eleven years. Of interest is the unusual picture of mucocellular adenocarcinoma.

CASE 11.—(Dr. J. B. Montgomery.) S. W., aged 49 years, multipara, was admitted Feb. 15, 1941. Presumptive diagnosis: fundal carcinoma, relatively early. There was a history of vaginal bleeding of one month's duration, the first to appear following an irradiation menopause of four years' duration. Cervix was intact, retroflexioversion of uterus with small myoma in fundus, and adnexa were negative. Because of the recurrent bleeding and suggestive history of malignancy, complete abdominal hysterectomy and bilateral salpingo-oophorectomy were performed on Feb. 19, 1941. Grossly there was no extension or metastasis from the uterus, the myometrium of which was deeply infiltrated by an adenocarcinoma of intermediate grade malignancy (Grade III). Uneventful recovery. Patient has remained well to date.

Previous Treatment.—Because of menorrhagia of seven weeks' duration thought to be due to fibromyomas in a patient aged 45, curettage and cervical biopsy were performed, and intrauterine radium (600 mg. hr.) was employed on Nov. 2, 1937. Sections from the biopsy revealed a benign erosion of the cervix. Those from the curettage presented a rather bizarre picture, nearly the entire stroma being replaced by numerous glandular formations with hardly any interglandular stroma in some places. The glands, unequal in size and dilatation, and lined by several layers of cells with centrally situated nuclei, could scarcely be called malignant. The lesion was termed "carcinoid hyperplasia" and Dr. Hoffman, who coined the phrase, warned that the patient be kept under close observation and that subsequent curettings be examined from time to time. This was done. Consequently recurrence of bleeding four years later was promptly observed and treated as noted.

Comment.—The admonition of the pathologist, combined with accurate clinical observation, resulted in radical treatment. The other point of interest is the designation of the original lesion as "carcinoid hyperplasia," which might be regarded by some as the equivalent of the term "papillary adenoma malignum" but which in our opinion is an atypical endometrial hyperplasia so marked as to histologically mimic the latter.

CASE 12.—(Dr. Anspach.) R. H., aged 44 years, nullipara, was admitted March 10, 1941, because of an attack of lower abdominal pain, accompanied with an enlargement of the uterus and left adnexa. Presumptive diagnosis: fundal carcinoma with accompanying chronic pelvic inflammatory disease. There was a prolonged history of antecedent vaginal bleeding with numerous curettements which will be described in detail. On March 13, 1941, complete abdominal hysterectomy, bilateral salpingectomy, and right oophorectomy were performed (the appendix and possibly the left ovary had been removed many years before). Stenosis was present at the site of the internal os, and the endometrial cavity was the site of an adenocarcinoma of low grade malignancy (Grade II) that deeply penetrated the myometrium (Fig. 6). A left hematosalpinx was present, the ovary being absent; the right adnexa were lightly adherent, but otherwise normal. There was no histologic evidence of metastases. Postoperative external irradiation followed, and the patient is apparently well a year later.

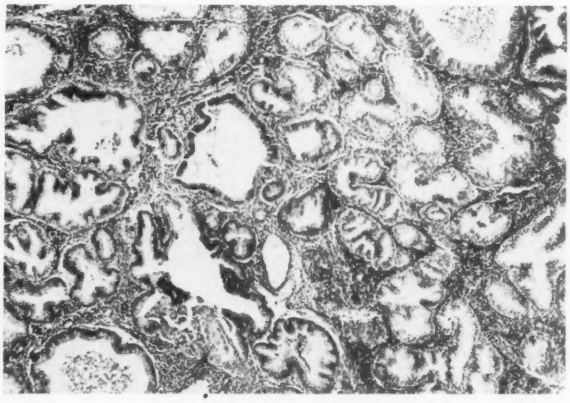


Fig. 5.—Case 12 (fundal group). So-called "carcinoid hyperplasia" discovered in 1933. (Photomicrograph ×50.)

Previous Treatment.—The earlier course of this patient and the treatment accorded is lengthy but unusually interesting. In September, 1918, at the age of 21, Dr. John G. Clark performed a curettage for irregular uterine bleeding. This helped for two months. In December, 1918, Dr. Clark again performed a curettage together with abdominal hysterotomy because of a possible uterine myoma; a cystic left ovary was either removed or punctured, and an appendectomy was done. A year later (1919), because of recurrent bleeding, curettage followed by 350 mg. hr. of radium, was employed. This treatment was repeated two years later (1921) when there was further recurrence. Dr. Sidney Dunne has been unable to find any record of sections from these various curettages, but evidently nothing of a malignant nature was suspected or found; very probably, in view of the history, the condition was one of typical hyperplasia as we know it today. For eleven years the patient remained well and had married. In 1932 (aged 35), menstruation again became irregular and Dr. Anspach performed a curettage on Nov. 11, 1932, the curettings showing a marked premenstrual function. A year later, for continued irregularity curettage was again resorted to, with a radium application (300 mg. hr.) on Nov. 14, 1933. There was a relatively slight enlargement of the uterus. Drs.

B. L. Crawford and Jacob Hoffman both felt that the lesion was most probably an adenocarcinoma of low grade malignancy (Grade II), although the diagnosis of "carcinoid hyperplasia" was tenable (Fig. 5). Sections were submitted to Dr. Charles Norris and to Dr. Joseph McFarland. The opinion of the former was that the lesion was benign but that in view of many extremely atypical features and because of the repeated bleeding, operation was advisable. Dr. McFarland's advice was essentially the same. Nevertheless, the husband, a physician, refused surgical treatment, and the patient was left alone. The symptoms then remained in abeyance for several years, but recurred in 1935, and on Dec. 12, 1935, Dr. Anspach again did a curettage and applied radium (300 mg. hr.). This curettage was similar in most respects to that reported in 1933, although it was conceded that the glands approached a more normal appearance. In view of the gratifying response to the previous irradiation, surgery was again refrained from. Curiously enough, the uterus became smaller, and the patient remained

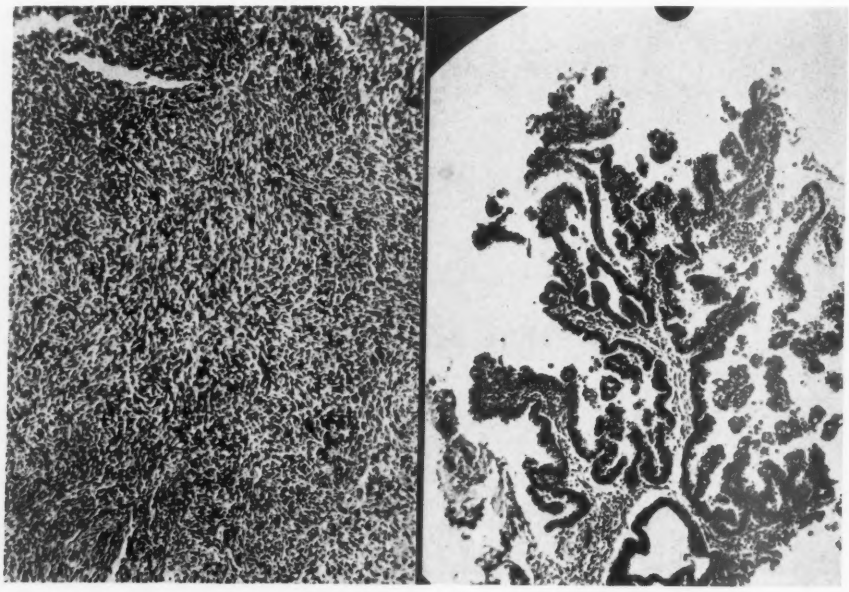
Fig. 6.—Case 12 (fundal group). Low grade malignancy (adenoma malignum, Grade II), revealed at operation in 1941. (Photomicrograph ×50.)

symptom free for six years, when at the age of 44, without external bleeding, pelvic pain and the discovery of a pelvic mass made operation imperative, and this decision was now concurred in by the husband, with findings as noted.

Comment.—Much could be said about this case. Granting an earlier condition of endometrial hyperplasia, it would seem that much trouble could have been avoided if the advice relative to operation in 1933 had been accepted, for the lesion was then regarded as very likely malignant on exceptionally strong grounds. It is astonishing to realize that relatively small radium dosage evidently retarded the growth of this possibly low grade carcinoma over a period of eight years. Another feature to be emphasized is that the stenosis of the cervical canal, evidently acquired during this period, seemingly prevented external bleeding for some time, so that an hematosalpinx resulted from the unreleased blood associated with the developing carcinoma, which finally caused sufficiently painful symptoms to warrant investigation and discovery of a pelvic mass.

Case 13.—(Dr. Scheffey and Dr. Nugent.) A. B., aged 71 years, multipara, was seen in consultation on May 1, 1941, because of vaginal

bleeding and colicky pelvic pain of six weeks' duration. Menopause occurred at the age of 42, with a subsequent history of bloody vaginal discharge beginning at 61, and appearing sporadically over an interval of six months (1931) when therapy effected a cessation of the symptoms. The present complaint was promptly managed by Dr. F. L. Nugent, who performed a curettage and applied radium (2,000 mg. hr.) at the Reading Hospital in April, 1941. (This had been preceded two years before by estrogenic therapy for six weeks.) The sections were reported as uterine sarcoma of high grade malignancy by the pathologist, Dr. E. D. Funk, and the patient was referred for an opinion as to future therapy in view of the author's previous knowledge of the patient (Fig. 7). Examination revealed an indurated, irregular but intact cervix, and a probe produced bleeding from the cervicouterine



A. *B.*

Fig. 7.—Case 13 (fundal group). *A*, Myosarcoma of uterus. *B*, Area in same section, suggestive of adenocarcinoma or hyperplasia. (Photomicrographs ×100.)

canal. The fundus was enlarged and somewhat fixed, with a sensitive nodulation in the cul-de-sac. Adnexa were not distinguishable. We were in complete agreement with the diagnosis made from the section submitted, and further irradiation therapy was advised. The patient died within three months, and autopsy revealed diffuse sarcomatosis of the abdomen, verifying the previous diagnosis of myosarcoma of the uterus.

Previous Treatment.—Diagnostic curettage followed by radium (1,200 mg. hr.), with removal of a cervical polyp, and cervical biopsy had been performed by the author on May 12, 1931, because of intermittent bloody vaginal discharge occurring twenty years after the establishment of the menopause. At that time, in addition to a cystocele and rectocele of moderate degree, the cervix showed old lacerations with slight eversion and polyp formation. The fundus was of normal size

and position and the adnexa were negative. The curettage showed hyperplasia of the senile endometrium and fibrosis of the stroma. The cervical tissue and polyp revealed nothing to suggest malignant change.

Comment.—Review of the earlier sections in comparison with the recent ones designated myosarcoma gave no indication of any relationship.

SUMMARY AND CONCLUSIONS RELATIVE TO THE FUNDAL GROUP

1. Nine of the patients were multiparas, 4 were nulliparas; the ages ranged from 43 to 71. Four patients were treated for fibromyomas (Cases 3, 9, 10, 11), 3 with radium and 1 with x-ray. Five were treated with radium, supposedly for postmenopausal functional bleeding (Cases 1, 2, 4, 7, 13), but in the first three of these the earlier records are incomplete. Two were treated for fibrosis uteri or functional bleeding (Cases 6, 8), and 2 for typical hyperplasia (Cases 5 and 12). Trachelectomy, hysterotomy, and cervical biopsy were accompanying procedures in 3 patients, respectively (Cases 5, 8, 10), and polypectomy with biopsy was performed in 2 patients (Cases 10, 13). Curettage accompanied the radium applications in all except the patient treated with x-ray, but no record of the examination of the curettings could be found in 4 of them (Cases 1, 2, 3 and 4).

2. An irradiation menopause was produced in 5 patients, ranging in age from 40 to 47 at the time of the initial treatment. None occurred in 2 patients aged 22 and 36, respectively. In 6 patients, from 50 to 61 years of age, the bleeding was postmenopausal, occurring from four to twenty years after its establishment. In no instance did the natural menopause occur after 50 years.

3. The time intervening between the benign treatment and the diagnosis of malignancy was 2, 2, 3, 3, 4, 6, 7, 10, 10, 11, 12, 13, and 23 years, respectively.

4. Myosarcoma occurred in one patient in the fundal malignancy group. Adenocarcinoma was eventually diagnosed in 12 patients, being early or only moderately advanced clinically in all but 3 of them. This proportion does not vary appreciably from the clinical extent of the lesions noted in our total series of fundal malignancies. In this particular group of patients, there were 4 with low grade, 3 with intermediate, and 5 with high grade malignancy. One intermediate grade lesion was unusual, a mucocellular adenocarcinoma.

There is no demonstrable relationship between the time interval following the initial irradiation therapy and the grade of malignancy that finally occurred; neither is there any between the age when the malignancy developed and its gradation.

As regards the final outcome, however, it is interesting to note that no patient with high grade malignancy survived treatment for more than three months to a year, and the same applies to the patient with myosarcoma. The 3 patients with an intermediate grade of malignancy have remained well from four months to a year and one-half; the 4 pa-

tients with low grade malignancy, from one to four years. These findings are in accord with our experience in the complete fundal carcinoma series.

5. Carcinoma was perhaps present in 6 patients at the time of the initial irradiation therapy. This assumption is very probably true in Cases 1, 2, and 4, where radium was applied with questionable curettage, since no record of the latter could be found and adenocarcinoma was definitely proved to be present within three years thereafter. Carcinoma was evidently present in Case 9 when x-ray therapy was administered for fibromyomas without diagnostic curettage and a low grade lesion was found within two years. In Cases 7 and 8, review of the original sections indicated lesions of low grade malignancy, the actual diagnosis being made six and thirteen years later, respectively, when irregular bleeding recurred. In these instances errors in judgment were evident.

In four patients in whom malignancy was discovered from 10 to 12 years later (Cases 3, 6, 10, 13), no errors of omission seem to have played a part, and the neoplastic process might be regarded as a late independent one.

Special interest attaches to the remaining 3 patients: In Case 5 radium therapy was twice used at the age of 36 to control proved hyperplasia, and seven years later a high grade adenocarcinoma was discovered, treated by hysterectomy, with death occurring a year and a half later with metastases.

In Case 11, "carcinoid hyperplasia" was diagnosed at 45 when radium was applied for a fibromyoma. Return of symptoms in four years was promptly treated with radical surgery and an intermediate grade of lesion was found. Patient living and well for more than a year.

In Case 12, implied hyperplasia was repeatedly treated with radium beginning at the age of 21. At 35 "carcinoid hyperplasia" or what some might call a low grade malignancy, was discovered and again irradiated; finally at 44 indisputable carcinoma was found at radical operation after the return of symptoms. This patient has remained well for over a year.

No criticism can be leveled at the management of Cases 5 and 11. Surgery would long before have been resorted to in Case 12 but for the repeated objections of the husband to radical operation.

6. In only two instances, Cases 7 and 8, have we factual evidence to indicate that radium may have retarded a malignant growth, for review of the curettings secured 6 and 13 years before when the radium was used to control supposedly benign bleeding, showed definitely malignant lesions. With recurrence of symptoms and repetition of curettage and radium therapy, adenocarcinoma of low grade malignancy was found present with an advance in abnormal morphologic structure. Even so it is admittedly an assumption to regard these malignant growths as quiescent over these years, for the appearance of a newer neoplastic process cannot be readily disproved. Attempting to draw

any conclusions relative to the primary effect of the earlier irradiation in retarding the development of malignancy in the other patients (excluding those in whom the condition was probably present at the outset, Cases 1, 2, 4, and 9), is equally fallacious, as is speculation relative to the initiation or acceleration of malignancy by irradiation in this series of patients. A statement of fact that can be made is this: The response to irradiation with radium has been more effective in the low grade and intermediate grade lesions than in those of the high grade variety, as evidenced by the surviving patients exhibiting the low and intermediate grades of malignancy.

7. The analysis of the fundal group emphasizes certain truths that are almost self-evident. Irradiation therapy should always be preceded by or accompanied with diagnostic curettage, and all curetted material, no matter how inconspicuous, should be thoroughly examined and carefully interpreted. Fibromyomas should never be regarded as the sole cause of postmenopausal bleeding until an accompanying adenocarcinoma of the endometrium has been ruled out. So-called functional or climacteric bleeding should be viewed with similar suspicion. Among 12 patients with adenocarcinoma pre-existing typical hyperplasia was reported twice, with definite proof in one instance; polyps were found twice, both being benign. Of special interest was the lesion that we have termed "carcinoid hyperplasia" present in one and possibly two patients in the series. The single patient with myosarcoma (Case 13) exhibited a prior senile type of hyperplasia and a benign cervical polyp.

DISCUSSION

This presentation has been centered upon a survey of the relationship between irradiation for supposedly benign conditions and the subsequent development of uterine malignancy. The role of cervical lesions, which some term "precancerous," has been appropriately mentioned with respect to the group of patients in whom carcinoma of the cervix developed, and certain conclusions have been stated. The controversial question pertaining to the association between endometrial hyperplasia and adenocarcinoma of the fundus has not been entered into in detail; its occurrence in a few of the earlier curettements has merely been stated as a fact.

In this respect, and apart from the irradiation phase of the problem, it is of interest to note that in the complete series of patients with fundal carcinoma, three records of previous curettements without irradiation therapy are available, and they may be recalled to advantage. In two of these women, treated for abnormal bleeding, an interval endometrium was present two and six years before, the former developing a high grade, and the latter a low grade malignancy at 50 and 45 years of age, respectively. The third patient, developing a low grade lesion at 68, had been curetted twelve years previously by Dr. G. M. Laws, who informed us that "glandular hyperplasia" had been found, but that

no sections were available for review. This case, added to those of two patients treated with radium, in one of whom preceding hyperplasia was a proved finding, and implied on good authority in another, makes a total of three instances of pre-existing typical hyperplasia in our complete series of 124 patients with fundal carcinoma. No statement can be made with respect to coexisting hyperplasia and adenocarcinoma, because sections of all the fundal malignancies observed have not been reviewed. The cystic hyperplasia found previously in the one instance of myosarcoma that occurred was typical of the senile endometrial pattern recently reported by Novak and Richardson, Jr.

Of serious concern to us has been the lesion that has been referred to as "carcinoid hyperplasia," a term that we have employed to describe atypical endometrial hyperplasia which is so marked as to resemble histologically the low grade lesion generally referred to as papillary adenoma malignum (Grade I), although there is no definite distinguishing feature that would label it as carcinoma. It might be regarded by some as an extreme grade of hyperplasia; by others as a very low type of malignancy. The stroma cells show mitotic activity. The glandular structures are greatly increased in number and, as in true hyperplasia, show a marked disparity in size. At times they may present bizarre convolutions. They are lined by several rows of cells which show mitotic activity. Proliferation of the cells may be so marked as to result in polypoid formations which extend into the lumina of the glands. A distinguishing feature is the sparsity of the stromal elements, as a result of which the glands lie very close to each other and almost fuse. Two such instances have been described (Cases 11 and 12) in which adenocarcinoma definitely developed later on. This experience has taught us to regard such lesions as essentially malignant and to manage them accordingly.

A decade ago Howard Taylor, Jr., stated in the summary of an exceptional survey of the subject that "whether from a practical standpoint, hyperplasia is to be regarded as precancerous and treated as such, must remain an open question." That the question still is an open one, is evident from the divergent views to which expressions have been, and continue to be given.

Eardley Holland, in discussing the paper of Norris and Behney on "Radium Irradiation for Benign Hemorrhage" in 1936 stressed the importance of learning whether or not radium in the uterus has any effect in increasing the incidence of fundal carcinoma. He felt that there was no such connection but believed that the possibility ought to be "definitely settled one way or the other." Similar and some opposing views have been expressed by others. With respect to the group developing cervical carcinoma, there was no evidence that irradiation per se had either retarded or accelerated its development. As regards the fundal carcinoma group, the only statement of fact that can be

made from this study is that malignant lesions of low or intermediate grade responded more favorably to irradiation than did those of high grade character. With respect to this observation, Healy, Burnam and others have repeatedly stressed the value of irradiation therapy either alone or preliminary to surgery in the treatment of fundal carcinoma. There was also reason to assume that in two cases at least, unrecognized lesions of low grade malignancy may have been held in abeyance for a considerable time. With regard to the lesions that were primarily benign, such a supposition is purely speculative. Norris has called attention to his experience in sectioning postradiated uteri, declaring that in most instances he was "unable to see anything under the microscope that indicated previous irradiation, other than senile changes which were general throughout the endometrium."

From the analyses of these two series of patients, it is our conclusion that errors of omission, either in technique or in judgment as commented upon, and not the irradiation therapy itself, were the responsible factors in the subsequent occurrence of malignancy in the particular instances mentioned; in the absence of such errors, the retarding influence of the irradiation is more or less speculative.

The lessons learned and the steps suggested to diminish the possibilities of similar developments have been outlined in the respective summaries and need not be repeated.

In the compilation and preparation of this work, I am not only indebted to my former chief, Dr. B. M. Anspach and to my immediate associates for their cooperation in supplying information, but to colleagues in other institutions who have similarly aided me, and these acknowledgments are mentioned throughout the text. Much of the pathologic material in years gone by was reported by the late Dr. Baxter L. Crawford, former pathologist to the Jefferson Hospital. More recently these studies have been made under the direction of Dr. C. J. Bucher, present pathologist to the Hospital with the active cooperation of Dr. Jacob Hoffman, departmental pathologist, who has helped considerably with the histologic interpretations.

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DISCUSSION

DR. CURTIS F. BURNAM, BALTIMORE, MD.—The necessity of a thorough preliminary examination cannot be emphasized enough, when using intrauterine radium. This applies to many other kinds of treatment, especially where bleeding or tumor is concerned. Certainly, a routine examination under anesthesia and a curettage should precede every hysterectomy, and especially supravaginal hysterectomies. Dr. Howard W. Jones, of our Clinic, has recently reviewed a series of 754 consecutive primary cancers of the cervix. Fifty-one of these, almost 7 per cent, were of the cervical stump. Sixteen, of the 51, developed within less than two years of the operation, slightly more than 2 per cent.

Our observations indicate that anaplastic carcinomas of the uterine body are much more radiosensitive than histologic low grade cancers. The outlook for clinical cures and survivals is, however, inversely proportional to the grade of malignancy, provided the disease is still limited to the uterus. Where the disease is beyond the uterus, a clinical cure is more likely with an anaplastic growth. Average survival is likely, however, to be longer in the low grade cancers.

The microscopic descriptions given by Dr. Scheffey are very interesting, but need little comment. The term "carcinoid" or "canceroid" in this connection is new to me, but the microscopic picture is an old and familiar one. Such conditions may persist unchanged for years. Often, if thoroughly curetted before a hysterectomy, no evidence of trouble is demonstrable in the removed organ.

We have done very little radiation for postmenopausal bleeding of benign origin, but have no evidence that it is harmful, or that it may not control bleeding. One must remember that even curettage may not disclose an existent cancer. Two cases illustrate this: (1) the first was a physician's wife who had had a curettage on two occasions with very small amounts of normal tissue obtained, after a further six months of bleeding she consulted another physician, who found a now enlarged uterus and abundant cancerous material. (2) The second case was that of a maiden lady with senile vaginitis, low ionizable blood calcium, and a small uterus. On account of bleeding she was curetted but no tissue could be obtained. For two months she was put on estrogen therapy and an appropriate regime to correct the calcium deficiency. The vaginitis cleared markedly, calcium levels reached normal, but bleeding continued. The uterus was still small, but abundant cancerous material was now obtained on a second curettage.

The question may be asked as to whether intrauterine radiation increases the probability of corpus, other gynecologic cancers, or cancer generally? One would think so, especially of cancer of the body of the uterus, rectum, and bladder. Having observed several endometrial cancers in our series about ten years ago, we have turned to x-ray for the treatment of benign bleeding. It has proved equally effective, more accurately controlled, and much more plastic in adjustment to each individual case.

Naturally, a starting point would be a knowledge of the frequency of cancer of the corpus. Very interesting vital statistics are available as to the occurrence of uterine cancers, but there is no accurate division between those originating in the cervix and body by any of the authorities I have consulted.

I have just analyzed 625 cases, treated with intrauterine radium, between January, 1912, and January, 1920. In this group, we have full records for more than ten years, and in nearly all for much longer periods. You will observe that in 625 cases there developed 25 malignancies, or a little less than 4 per cent. Their distribution was as shown in Table I.

Having no other source of information, I have attempted to estimate the relative percentages of cervix and body cancers as they have occurred in our clinic: In 5,173 cases, taking all ages, the cervix cases constituted a little more than 87 per cent, the corpus cases over 12 per cent, and sarcomas less than 0.9 per cent. Taking only patients aged from 55 up the ratio between body and cervix cancers is ap-

TABLE I

	NUMBER OF CASES	PERCENTAGE	TIME OF DEVELOPMENT	
Cancers of the body of the uterus	5	0.8	1– 6 yr.	2–12 yr.
			1–14 yr.	1–17 yr.
Sarcoma of the body of the uterus	1	0.16	12 yr.	
Cancer of the cervix	3	0.5	2– 4 yr.	1– 8 yr.
Cancer of the vulva	3	0.5	1–10 yr.	1–16 yr.
				1–21 yr.
Cancer of the ovary	1	0.16	7 yrs.	
Cancer of the breast	7	1.12	1– 5 yr.	2– 8 yr.
				1–18 yr.
				1–14 yr.
				1–20 yr.
Other cancers	4	0.64		
	1 Small bowel		4 yr.	
	1 Large bowel		9 yr.	
	1 Tongue		7 yr.	
	1 Liver		23 yr.	

proximately as 1 to 2. From the sources we draw our material, practically all cervix cases are referred to us, but a good many corpus cancers are not. I would venture to guess that from the age of 55 and over, corpus cancers are at least as common as cervical cancers.

It is of interest that only 1 out of 6 of my cases of corpus malignancy developed in less than 12 years of the original radiation treatment, whereas Dr. Scheffey had 10 out of 13.

I believe the ordinary use of intrauterine radium for benign conditions does not cause an increase in body, cervical, or other cancers. The total cancer mortality closely approximated, taking age into consideration, is that found in the papers on vital statistics.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—Dr. Scheffey's paper presents an interesting topic for our consideration and at the same time he asks an important question. Is there an etiologic relationship between the application of radium in the treatment of benign uterine lesions and the occasional subsequent development of a malignant lesion such as cancer in the same organ?

I agree fully with his conclusion that in his reported cases there is no evidence to support such an opinion. This question has been raised from time to time heretofore by others, not only with regard to the therapeutic use of radium but also regarding x-ray therapy.

The unusually large opportunity which I have had in the past twenty-one years to observe the effects of radiation therapy as utilized in the treatment of human tumors, has presented me with many instances of the occurrence of multiple primary tumors in the same individual and frequently in the same organ. Often these tumors have been coincidental, at other times one type of growth has preceded the other by an interval of time varying from months to many years.

Probably the most common combination of tumor types have been uterine fibroids and benign breast lesions. Following these, I would place uterine fibroids and carcinoma of the corpus, and next in order uterine fibroids and carcinoma of the breast. Carcinoma of the cervix in spite of its great frequency is seldom associated with other histologic types of tumor, which is interesting since uterine fibroids are so common that one would expect a frequent association of the two tumor types.

It is evident that uterine fibroids represent the common denominator and the other types of tumor are the variables. I have a feeling that in human beings, as in animals, we have tumor-bearing individuals or strains, families if you will. How common it is for a gynecologist to operate upon each of several sisters in a family for fibromyomas.

The radiation dosage used in the benign lesions of the corpus in general was much less than would now be regarded as adequate for the conditions treated. This is, however, understandable as some of these cases were treated at a time when our knowledge of radiation effects was not well defined.

Regarding his cases of corpus carcinoma, I would like to comment upon Case 12 with a pathologic report on the curettings of "carcinoid hyperplasia." Such a report is unsatisfactory to a surgeon and suggests an uncertain frame of mind on the part of the pathologist. That uncertainty should have been enough to require the gynecologist to increase the radium dosage or remove the uterus. The pathologist cannot in every case give us an exact histologic diagnosis, but he can report doubt or suspicion on borderline cytologic changes or pictures. The responsibility for the proper treatment of the case rests with the gynecologist.

Incidentally, may I say that nowadays it is well recognized that intrauterine dosages of radium below 1,000 mg. hr. or moderate dosages of x-ray may retard growth activity in so-called low grade endometrial cancers such as adenoma malignum grades 1 or 2 for several years, during all of which time the patient may be symptom free. This explains why Dr. Scheffey found that some of his patients, even some years after their radiation treatment, were still fair risks for operation.

The patients with the higher histologic types of cancer, of course, were unfortunate and failed to survive later treatment by radiation or surgery as the original radiation dosage was far too inadequate for that histologic grade of cancer.

Finally, I think as specialists in diseases of women we should be meticulous to a fault in the treatment of benign cervical lesions and benign uterine bleeding with or without fibromyomata in women of any age. If radiation methods have been used to treat the benign lesion, I would advise against discharging such a patient from observation two or three years later because she is symptom free and the pelvic organs appear to be normal. I think it would be much better to encourage such patients to report once a year for a check-up.

DR. CHARLES A. BEHNEY, PHILADELPHIA, PA.—In administering radiologic treatment for benign hemorrhage the gynecologist assumes the responsibility of ruling out carcinoma. The importance of routine histologic examination of ample specimens from diseased cervices is convincingly demonstrated in Dr. Scheffey's presentation. Even when biopsy is practiced, the sample is often inadequate and diagnostic curettage should be more than a few scrapings from the lower uterine segment. The chance of a small growth evading the curette or the biopsy scalpel can never be entirely eliminated, but if this possibility is always remembered, the potential error can be reduced. A satisfactory biopsy from the cervix should consist of a wedge which includes a portion of the cervical canal, the diseased area and some adjacent healthy tissue. In order to determine the exact origin of a malignant tumor of the uterus, we have found it useful to secure three separate specimens for microscopic study. The first consists of curettings from the cervical canal to the internal os; the second from the uterine cavity above the internal os; and the third, a generous specimen from the cervix. In this way there is less danger of mistaking an adenocarcinoma originating in the cervical canal for fundal malignancy. One should endeavor to explore every part of the uterine cavity with the curette, paying particular attention to the top of the endometrial cavity and the cornua. Dr. George Gray Ward has devised special curettes better to reach the more inaccessible parts of the uterine cavity.

Dr. Scheffey's case of low grade carcinoma, proved to be of at least thirteen years' duration, again demonstrates that the life cycle of carcinoma may be much longer than was generally supposed.

In 1936, Dr. Charles Norris and I reported the results of radium irradiation for benign uterine bleeding to this Society. Our series, from the gynecologic service of the University Hospital, comprised 687 cases of myomas of the uterus, and 750 cases of myopathic hemorrhage, a total of 1,437 patients. Of these, 1,006

were followed up for two or more years, and 300 (184 myoma uteri and 521 functional hemorrhage cases) for from ten to twenty years after treatment. In this series, uterine carcinoma was discovered subsequently eight times, an incidence of about 0.8 per cent. Carcinoma was also found once in each of the following situations, the ovary, the bladder and the rectum.

Radiologic treatment of uterine bleeding, presumed to be of benign origin, should be practiced only after careful investigation of the cervix and fundus, and patients so treated should be followed up at regular intervals for the rest of their lives. When symptoms recur, hysterectomy rather than re-irradiation is the procedure of choice.

DR. ISIDOR C. RUBIN, NEW YORK, N. Y.—Two points may be made with regard to prophylaxis against neglected or undiscovered carcinoma of the uterus. First, diagnostic curettage in the presence of a carcinoma of the uterus may cause it to spread into deeper parts. Second, diagnostic curettage often fails to reveal intrauterine lesions, including submucous fibroids, polyps, and carcinomas. For these reasons I have felt it necessary to resort to x-ray visualization of the endometrial cavity, using a viscous, soluble, crystalloid iodine solution in cases of postmenopausal bleeding when one suspects a polypoid condition or carcinoma. This substance needs to be introduced only in the small amounts of 1.5 to 2.0 c.c. In our service we have turned to this substance because of the bad reactions obtained from lipiodol. In several instances we have in this way revealed the presence of submucous polyps or cornual carcinoma which was missed on a previous curettage.

DR. JOHN A. MCGLINN, PHILADELPHIA, PA.—We have heard about the many cases which have been treated with radium without thorough investigation. This Society should also take cognizance of the present practice of treating benign bleeding with hormones. A woman who is bleeding from the uterus deserves the most careful investigation and no one is justified in using radium, still less a substance given by hypodermic injection, without previous careful examination. We will often miss carcinoma which might have been recognized early simply on account of the modern treatment of hemorrhage by hormones.

DR. SCHEFFEY (closing).—Dr. Healy and Dr. Burnham have a right to object to the term "carcinoid hyperplasia." It is not my intention to attempt to introduce a new term into the literature, but merely to describe a controversial lesion. The designation "carcinoid hyperplasia" was suggested by our departmental pathologist, Dr. Hoffman, and is used to describe those curettings about which there is so much doubt regarding proper classification. Some may consider such a lesion as definitely malignant, calling it "papillary adenoma malignum"; others may regard it as extreme hyperplasia, as was the case in this particular instance. What we have learned practically from this experience is that when we do encounter a lesion such as this we shall not hesitate to regard it primarily as malignant and treat it accordingly.

The systematic follow-up of all patients who have had irradiation for benign conditions has been properly emphasized by all of the discussors, and I know that our experience has made us more conscious than ever of the importance of continued attention to patients following such therapy.

Dr. Behney has approached the problem somewhat differently, showing the subsequent occurrence of one cervical and of seven fundal carcinomas in 1,006 patients treated with irradiation for benign conditions. I agree with him entirely in the careful technique that he has outlined for securing adequate tissue from all sources of the uterus by thorough curettage and biopsy.

Dr. McGlinn brought up the question of indiscriminate hormonal therapy and I agree with him heartily in his denunciation of it. In our experience we have seen too frequently the loss of valuable time because injections of hormones have been used thoughtlessly to control abnormal menopausal and postmenopausal bleeding without adequate examinations.

THE FUNCTIONAL ANATOMY OF LABOR, WITH SPECIAL REFERENCE TO THE HUMAN BEING*

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(From the Department of Physiology and Pharmacology, Northwestern University Medical School)

THE primate uterus is a highly differentiated structure and, from the viewpoint of functional anatomy, presents six more or less distinct problems: (1) the cause of the onset of labor;[1-4] (2) the mechanism of polarity;[4-6] (3) the mechanism of the coordination of the fused longitudinal halves; (4) the mechanism of "retraction";[7] (5) the mechanism of the dilation of the cervix;[8-12] and (6) the mechanism of the separation of the placenta.[13, 14]

The objectives of this paper are: (1) to correlate the course of the wave of contraction with the morphologic pattern of the uterine musculature in the human being; (2) to summarize the evidence regarding the growth of the isthmus uteri and its unfolding and inclusion as a part of the general uterine cavity during pregnancy in the human being and monkey; and (3) to report certain observations resulting from measurements made on all the frozen sections of the human uterus reported in the literature.

I. THE WAVE OF CONTRACTION AND THE ARCHITECTURE OF THE UTERINE MUSCULATURE

The Wave of Contraction.—In 1930, Ivy, Hartman and Koff[10] directly observed the contracting primate uterus of the rhesus monkey in labor. The typical wave of contraction consists of two waves which start bilaterally and synchronously from an area located in the region of the insertion of the Fallopian tubes. The areas (the "pace-makers") are located about 1.5 cm. ventral and cranial to the insertion of the tubes. The areas appear to be constantly quiescent in that they do not blanch during uterine contraction. The wave on each side spreads as a widening wave, elliptical in form. As the wave from each longitudinal half of the uterus approaches the midline the corpus is observed to shorten longitudinally and a circular contraction appears at the level of the insertion of the round ligaments. This circular wave of contraction moves caudalward over the lower segment and finally involves the cervical sphincter. The spread of the wave of contraction is diagramed in Fig. 1.

It was quite evident that the musculature in the region of the placental site is less involved in the contraction than the remainder of the uterus. Occasionally a wave of contraction was observed to be initiated only on one side, producing a bulging of the opposite side or an obliquity

*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

of the uterus. Such an atypical wave of contraction sometimes passed to the opposite side and again died out at the midline.

Hofbauer[15] has described a somewhat similar wave of contraction in the human uterus, which he observed during a cesarean section under spinal anesthesia and after the intramuscular injection of pituitrin. His description differs from ours chiefly in regard to the site of origin of the wave of contraction which he placed in the midline rather than in the region of the insertion of the tubes.

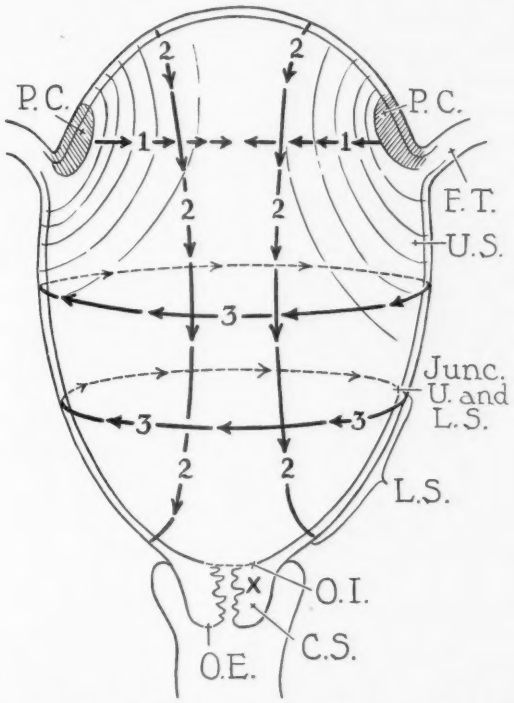

Fig. 1.—A diagram illustrating the passage of the wave of contraction over the primate uterus of the rhesus monkey. *"1"* represents the waves that spread from the area (*P.C.*, pacemaker) slightly above and ventral to the insertion of the tubes; *"2,"* the longitudinal shortening that occurs as the orbicular, *"1,"* waves reach the midline; *"3,"* the circular peristaltoid wave that is seen to start near the insertion of the round ligaments and travels downward to involve the cervical sphincter located in the region of the obstetrical internal os (*I.O.*).

The Architecture of the Human Uterine Musculature.—When we originally described the wave of contraction, a complete study regarding the architecture of the primate uterine musculature was not available. Therefore, Ivy, Hartman, and Koff[10] could not satisfactorily correlate the structure of the myometrium with the mode of travel of the wave of contraction. It was pointed out, however, that the mode of origin and travel of the contraction wave correlated with the mode of travel that one might anticipate from a consideration of comparative anatomy and physiology.[5-7, 16]

In the meantime, Goerttler[17] has published a complete study of the architecture of the human myometrium. The results of his study, though they require confirmation, correlate well with our description of the mode of travel of the wave of contraction.

Goerttler made thick sections of fresh fetal, mature, pregnant, and nonpregnant human uteri. The sections were dehydrated by a special process and carefully stretched to separate slightly the fibers. The sections were then dusted with graphite or gold bronze dust. The excess was removed and the sections were examined in intense light. This permitted a detailed study of the course of the muscle fasciculi.

His observations, which are most pertinent to the present discussion, follow. The myometrium is composed essentially of two interlacing, spiral systems of muscle fasciculi. The origins of these two systems are traced to the unfused Müllerian ducts. The diagrams of the disposition of the two muscular systems are shown in Fig. 2. They have a striking

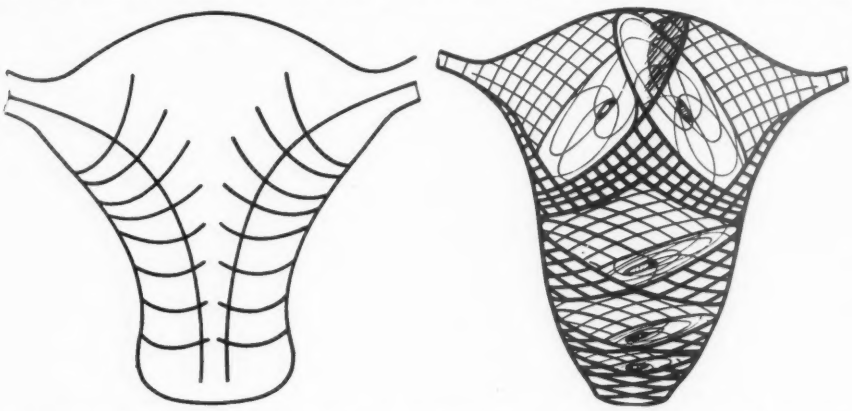

Fig. 2.—Diagrams, redrawn from Goerttler, illustrating his findings on the arrangement of the two chief systems of muscular fasciculi in the nonpregnant uterus, which result from the fusion of the Müllerian ducts. The diagrams should be compared with the route of travel of the contraction wave, as illustrated in Fig. 1.

similarity with our description of the mode of travel of the wave of contraction in the monkey's uterus. Some of the older anatomic descriptions of the uterine musculature, also show the orbicular arrangement of muscle fasciculi about the insertion of the tubes.

Comment.—Thus, a structural as well as a comparative anatomic and physiologic background appears to exist for the described mode of travel of the wave of uterine contraction in the primate uterus.

II. THE GROWTH AND UNFOLDING OF THE ISTHMUS UTERI IN PREGNANCY

In briefly reviewing and summarizing the evidence regarding the growth and unfolding of the isthmus uteri in pregnancy, one is interested in answering three questions: (1) Does the isthmus uteri grow and unfold to become a part of the uterine cavity in pregnancy? (2) Does it form only a part of the lower uterine segment? or (3) Does it form the entire lower uterine segment during pregnancy? How much the true histologic cervix contributes to the lower segment in labor is a separate question.

A. THE MONKEY

When Rudolph and I[6] described the mechanism of parturition in the bicornuate uterus of the dog, it was suggested that the fused portion

of the canine uterus was homologous with the isthmus uteri of the human uterus. The evidence for the homology was derived solely from a consideration of the embryology and the comparative anatomy and physiology of the uterus. A similar induction was made by Ivy, Hartman and Koff[10] when they described parturition in the rhesus monkey.

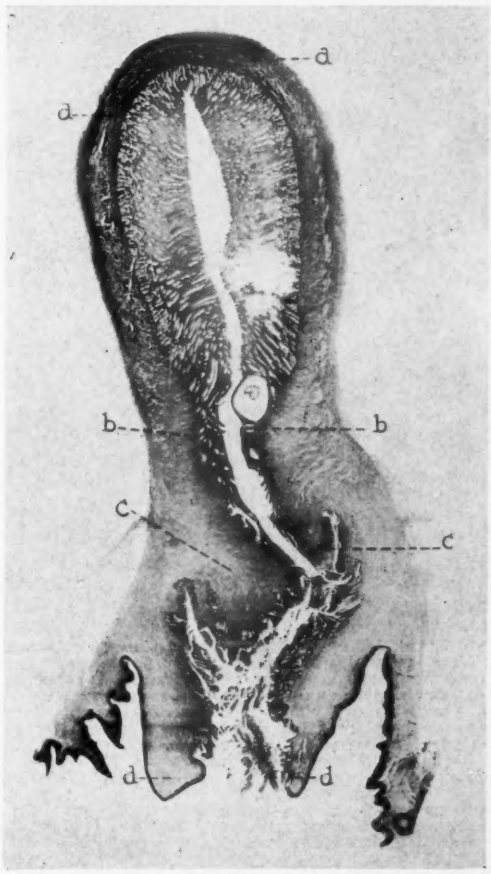

Fig. 3.—Sagittal section of the nongravid uterus of the rhesus monkey. "*b*" indicates the junction of the corpus with the isthmus [orificium isthmi internum (Stieve), or os internum anatomicum (Aschoff)]. "*c*" indicates the junction of the isthmus with the true histological cervix [orificium isthmi externum or orificium canalis cervicis internum (Stieve), or os internum histologicum (Aschoff)]. "*d*" indicates the external os [orificium canalis cervicis externum, or orificium uteri externum (Stieve)]. A small cyst, which is rather common in the human isthmus (ref. 20), is seen at the level of the internal orifice of the isthmus. True cervical glands are evident up to "*c*." Between "*c*" and "*b*" typical isthmic mucosa occurs. It is to be emphasized that the internal cervical lips, designated "*c*" constantly mark the obstetrical internal os during the latter part of pregnancy and labor in the monkey.

Anatomic evidence is now available which proves that in the primate uterus of the monkey the isthmus uteri grows and unfolds to become a part of the general uterine cavity during pregnancy. This evidence will be briefly presented.

The Parts of the Monkey Uterus (Macaca rhesus and *Macaca cynomolga).*—The uterus of Macaca is very definitely divided into three parts.[18, 19] The specialized epithelium of the true cervix is different from

that of the isthmus, and that of the isthmus is different from that of the corpus. A glance at Fig. 3 shows that the difference may be recognized grossly in a thin sagittal section.

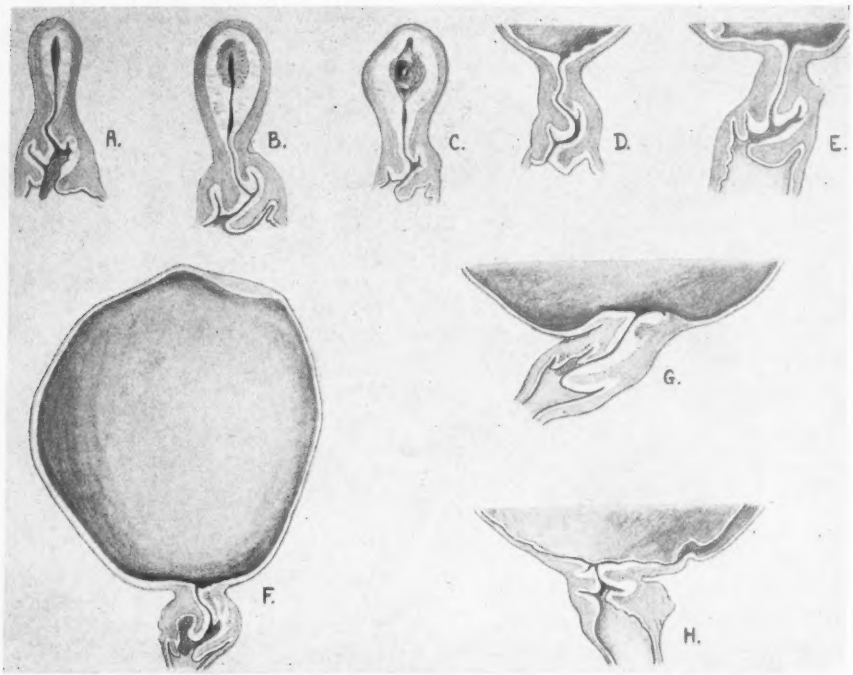

Fig. 4.—A copy of Franke's[19] specimens showing the growth and then the unfolding of the isthmus into the general uterine cavity in pregnancy. *A*, 16-celled ovum is present in tube; length of uterus is 3.6 cm.; A-P diameter is increased. Note internal and external lips of cervix, isthmus, and hyperplasia of mucosa of corpus. *B*, anterior and posterior placentas are visible; length of uterus is 4.6 cm.; A-P diameter is 1.7 cm. There is no decidual reaction in isthmus; mucosa of cavity is greatly thickened. Note internal and external lips of cervix. *C*, embryo and 2 placentas are visible; length of uterus is 3.8 cm., A-P diameter is 1.9 cm. In this specimen the decidual reaction extends into upper portion of isthmus. External and internal lips are evident, though anterior and exterior lip is small. *D*, fetal parts have been removed; length of uterus is 6.5 cm.; A-P diameter is 3.3 cm. The isthmus is longer than normal. The interior and exterior cervical lips are evident. *E*, fetal parts have been removed; length of uterus is 7.1 cm.; A-P diameter is 4.0 cm. The isthmus is still quite long. *F*, fetal parts have been removed; length of uterus is 8.45 cm.; *A-P* diameter is 6.3 cm. The isthmus has obviously unfolded. Note the interior and exterior lips of the cervix. *G*, fetal parts have been removed; length of uterus is 11.6 cm.; A-P diameter is 8.0 cm. The external cervical lips still hang like tongues downward; the internal cervical lips are now more horizontal, the isthmus having unfolded. *H*, fetal parts have been removed; length of uterus is 11.3 cm.; A-P diameter is 8.5 cm. Both cervical lips now lie horizontally. It is more typical for the internal lip to lie horizontally and the external lips to hang downward, as will be noted in the frozen sections of Danforth, Graham and Ivy.[18] In *F*, *G*, and *H* the internal lips of the cervix form the obstetric internal os.

The Obstetric Internal Os Is Grossly Labeled in the Monkey.—The crucial proof that the isthmus grows and becomes included in the general uterine cavity in the monkey rests chiefly on the fact that Nature has grossly labeled the obstetric internal os, or the junction of the true histological cervix with the histological isthmus. The macaca uterus has two cervical lips, an internal and an external (Fig. 3). The external lip forms the external os. The internal lip marks the site of the obstetrical internal os in the nonpregnant, pregnant and laboring organ[18] (see Fig. 4).

The Isthmus Uteri of the Nongravid Monkey.—The mucosa of the mesial aspect of the external lip contains typical mucous secreting cervical glands. This is true also of the inferior and inferior mesial aspects of the internal lip. The mucosa of the cranial mesial portion of the internal lip, where the mucosa of the isthmus begins, does not contain mucus-secreting cells or glands (Fig. 3, and ref. 19). The mucosa of the isthmus extends upward for a distance of 6 to 10 mm., according to our observations, where it joins the definitely thicker mucosa of the corpus. The point of transition is histologically quite definite.

The Isthmus Uteri of the Monkey in Pregnancy.—According to Franke,[19] the mucosa of the isthmus of the monkey manifests only a slight decidual reaction. An inspection of Fig. 4 shows that early in pregnancy the isthmus retains its general form. As pregnancy advances it grows in length and becomes included into the general uterine cavity so that the internal lip, lying in a horizontal plane, forms the obstetric internal os. This was confirmed[18] in our frozen sections of the monkey prior to the onset of labor.

Since the pregnancies of Franke's specimens were not dated, the time of initiation and completion of the unfolding of the isthmus cannot be stated. However, the isthmus has almost completely unfolded when the total length of the uterus has increased 2.6 times.

CALCULATION

1. Average length of non-gravid uterus (ref. 18) 3.2 cm.
2. Average length of gravid uterus at almost complete unfolding[19] 8.45 cm.
3. Calculation: $8.45 \div 3.2 = 2.6$ times increase in length.

Comment.—The evidence showing that the isthmus uteri unfolds and is included in the general uterine cavity of the uterus of the monkey is clear-cut and decisive. Thus, the isthmus uteri in the monkey either contributes to the formation of the so-called lower uterine segment, or actually is the lower uterine segment.

Whether the isthmus forms the entire lower uterine segment, exclusive of the cervix, is not known. We hope to settle this question by placing some nonabsorbable material in the musculature at the level of the physiologic retraction ring and locating its site in the involuted uterus.

The Extent to Which the Cervical Lips Contribute to the Lower Uterine Segment in Labor.—The internal cervical lip in the monkey, when it is effaced and dilated in labor, contributes a small but variable part to the lower uterine segment. The external lip is generally retracted beneath and external to the internal lip. Sometimes, however, the internal lip is markedly separated from the external lip, so that a wall of 1.0 to 1.5 cm. intervenes between the base of the internal and external lip. This is particularly true posteriorly (see Figs. 8 and 9, ref. 18).

THE HUMAN

The evidence for the growth, unfolding and inclusion of the isthmus uteri into the general uterine cavity in pregnancy in the human being is perhaps not as clear-cut and decisive as in the monkey. The reasons for this apparently are: (A) The isthmus of the nongravid human uterus, as identified histologically, is relatively less extensive than in

the monkey. (B) The site of the obstetric internal os or the upper limit of the true histologic cervix is not grossly labeled in the human being, though it is histologically labeled until the second stage of labor is approached. (C) In the process of full-term labor much of the true cervix mucosa is stripped off.[18, 19]

The Isthmus of the Nonpregnant Human Uterus.—The histology of the human isthmus has been described by numerous investigators.[11, 12, 20-25] The mucosa of the isthmus is much like that of the corpus, except that it is much thinner and the glands are more sparse. It manifests relatively little menstrual and decidual reaction.

The length of the human isthmus is apparently subject to considerable variation in the nongravid state. Aschoff gives a length of from 7 to 10 mm.; Stieve, of 4.5 mm.; Frankl, 5 to 9 mm.; Sabotta, 5 mm.; Oertel, 8 mm.; and Acosta-Sison, 7 to 10. According to our estimates the isthmus of the monkey (Macaca) makes up about 20 per cent and that of the human being (average 7.3 mm.) about 10 per cent of the total length of the nonpregnant uterus.

The Growth and Unfolding of the Isthmus in Pregnancy.—Stieve,[11, 12] who has made the most extensive study, finds that the isthmus increases in length two to three times before it unfolds to be included in the general uterine cavity. I have summarized and tabulated the data he presents. It is presented in Table I. The data show that during the first four to ten weeks of pregnancy the isthmus elongates two to three times, depending on the average length taken for the isthmus in the nongravid state.

A. Histologic Studies.

1. *The Mucosa:* In view of Stieve's studies, and those of others,[22, 25] on the mucosa in the region of the obstetrical internal os, the isthmus unfolds and is included in the general uterine cavity between 10 and 12 weeks of pregnancy. Then, the upper limit of the true histologic cervix is at the level of the obstetrical internal os (Table I). *This, I believe, constitutes the strongest type of evidence in support of the unfolding of the isthmus in pregnancy in the human being.*

2. *The Musculature:* Goerttler,[17] in his histologic studies of the muscular fasciculi of the human uterus, made studies on the gravid and nongravid human uterus. He reports that in the nongravid uterus the "circular" muscular of the isthmus lies almost horizontal (Fig. 2). In the gravid uterus as pregnancy advances the muscular fasciculi assume a steeper course. In the cervix, however, the circular or horizontal architecture of the fasciculi persists through pregnancy. In the corpus, the architecture is not significantly modified in the pregnancy. This evidence indicates that the growth and unfolding of the isthmus in pregnancy results in a modification of its architecture. It supports the evidence derived from a study of the mucosa of the obstetric cervix at different stages of pregnancy.

3. *The Membranes:* The relatively loose attachment of the membranes to the lower uterine segment has been used in support of the view that the isthmus forms the lower segment. Stieve,[12b] who believes that the isthmus forms the entire lower segment prior to labor, makes the following points: (a) the membranes are loosely attached to the lower segment; (b) the muscular wall of the lower segment is thinner through-

TABLE I. ANALYSIS OF STIEVE'S CASES (34), ABNORMAL AND INCOMPLETE CASES BEING OMITTED

LENGTH OF FETUS MM.	CASES	WEEK OF PREG.	UTERUS			CX. + IS. MM.	CX. MM.	IS. MM.	VERT. EXT. LENG. OF CAVITY MM.	CONDITION OF ISTHMUS
			LENG. MM.	BREAD. MM.	THICK. MM.					
Nonpregnant		Nulli	68	49	27	32	27	5	36	
Nonpregnant		Multi	78	55	31	34	27	7	44	
2.8- 10.8	4	4-5	93	81	75	36	26	10	57	Isthmus not unfolded
14.5- 27.0	6	6-8	104	80	67	42	29	13	62	Isthmus not unfolded
39.5- 52.5	6	9-10	124	83	72	43	28	15*	81	Isthmus not unfolded
64.0	1	11	133	82	75	--	35	--	98	Isthmus unfolded
82.0- 92.0	4	13	142	105	95	--	33	--	109	Isthmus unfolded
96.0	1	14	152	114	107	--	36	--	116	Isthmus unfolded
108.0	1	15	161	116	111	--	34	--	127	Isthmus unfolded
114.0-119.0	3	16	166	120	106	--	37	--	129	Isthmus unfolded
146.0	1	20	206	135	124	--	38	--	168	Isthmus unfolded
151.3-157.0	2	21	200	139	127	--	36	--	164	Isthmus unfolded
165.0-172.0	3	22	194	133	111	--	30	--	164	Isthmus unfolded
182.0-188.0	2	23	221	156	139	--	28	--	193	Isthmus unfolded

Isthmus of the nonpregnant uterus varies from 4.5 to 10 mm. in length: Aschoff (0.7-1.0); Frankl (0.5-0.9); Oertel (0.8); Sabotta (0.5); Acosta-Sison (0.7-1.0); Stieve (0.45).

*Longest isthmus Stieve found in pregnancy before unfolding was 22 mm. Note that during four to eleven weeks no change in breadth or thickness of uterus occurred on the average, but there is an increase in length. After isthmus unfolds, there is an increase in breadth and thickness. (Stieve, H.: Ztschr. f. Mikr.-anat. Forsch. **11**: 291, 1927; **14**: 549, 1928.)

out pregnancy (this may be questioned by frozen section evidence) and labor than that of the corpus; (c) the true cervix does not enlarge in pregnancy as does the isthmus and corpus; (d) the mucosa of the lower segment in late pregnancy is thin, there are no decidual cells and the epithelial cells are flat and the spongiosa is thinner; (e) the amnion and chorion are thinner over the lower segment and are tough due to connective tissue. These points are generally recognized as being true. However, it is difficult, if not impossible, after the isthmus has unfolded, to identify a clear-cut line of demarcation between the upper and lower segments. The evidence regarding the membranes is only suggestive. It is only corollary in my opinion to the other more conclusive histologic evidence, showing that, as pregnancy advances, the isthmus unfolds.

B. Gross Anatomic Evidence of the Unfolding and Growth of the Isthmus in Pregnancy. If the isthmus of the human being grows and unfolds and continues to grow to form the lower uterine segment, there should be some gross anatomical evidence of these changes.

1. *Hegar's Sign:* As early as 1893, Dickinson,[27] in describing the early signs of pregnancy, referred to Hegar's sign as being due to the compressibility of the isthmus or lower uterine segment. About four to seven weeks after the last menstruation, on bimanual examination, the compressible isthmus is found between the hard cervix and the elastic body of the corpus. This sign may, however, be due to the softening and increase in the diameters of the cervix. The sign is only corollary evidence in that it might be expected to occur at six weeks when the isthmus has grown appreciably (Table I).

2. *Changes in Form and Growth of the Uterus During Pregnancy.*— It was thought that if the isthmus grew in length and then unfolded some significant change in the form of the uterus might occur. To examine this possibility, frozen sections made during the early months of pregnancy were measured and Stieve's data were analyzed.

First, as indicated above, we know when the isthmus unfolds in the monkey, because the junction between the true cervix and isthmus is grossly as well as histologically labeled. It has almost completely unfolded when the length of the gravid uterus has increased 2.6 times over the nongravid length.

In the human being, using Stieve's data, the isthmus was unfolded when the length of the uterus had increased approximately 2 times ($14.0 \div 7.3 = 1.9$ times). Inspection of the frozen sections (Table II), without microscopic evidence, indicates that the isthmus appears to be unfolded completely in the four-month sections when the uterus has increased in length, 2.2 times ($16.3 \div 7.3 = 2.2$ times); whereas, in the five-month sections when the uterus has increased in length 2.9 times ($21.0 \div 7.3 = 2.9$), the isthmus appears to be unfolded. This evidence is only of interest in that it checks well with the more definite evidence on the monkey.

Second, after the initiation of pregnancy the length of the uterus increases continuously to term (Tables I and II, and Fig. 5). The uterus also increases in breadth and thickness (anteroposterior diameter) during the first four weeks (Table I and Fig. 6). But, according to the data in Table I, the uterus does not definitely increase in breadth and thickness during the period of from four to eleven weeks; then, a definite increase in breadth and thickness occurs (Table I and Fig. 6). It would appear that something occurs at eleven or twelve weeks which rather suddenly results in an increase in breadth and thickness of the

uterus. This is coincident with the unfolding of the isthmus, as indicated by the histologic studies of the mucosa.

It should also be noted (Table II) that the distance between the lower edge of the placenta and the internal os rather suddenly increases between the third and fourth months.

Third, one may expect the unfolding of the isthmus to cause a change in the rate of growth and possibly in the form of the uterine cavity. The ratio of the length of the uterine cavity to its sagittal circumference as shown in Table II may be taken as an indicator of the form of the uterine cavity. By the fourth month, the cavity has assumed the shape which it maintains to term. This may be an indication that the unfolding of the isthmus is completed at this time.

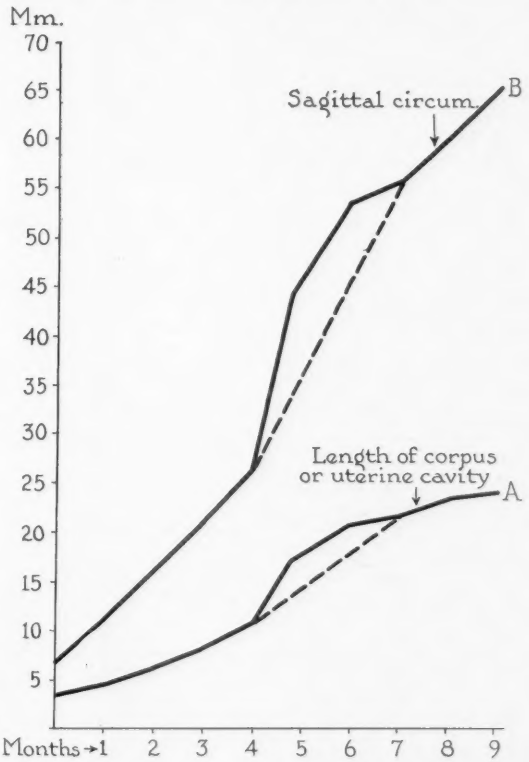

Fig. 5.—Curves of the growth in the length and the sagittal internal circumference of the corpus or general uterine cavity in various stages of pregnancy. Note the marked increase which occurs between the fourth and sixth month. Curves constructed from data (Table II) from frozen sections.

Changes in the rate of growth of the uterine cavity reveal another possibility. A study of Fig. 5 will show that there is a sudden increase in the growth rate during the fourth to sixth months. If one assumes first that the lower uterine segment is made up of the isthmus uteri, and second that the isthmus reaches its final length before it begins to unfold, one can account for this sudden increase in growth rate by an unfolding of the isthmus and its addition to the circumference of the uterine cavity:

1. Average length of lower uterine segment = 7.3 cm.
2. Circumference length of lower uterine segment = 14.6 cm.

3. Increase in sagittal circumference between 4th and 6th months = *26.9* cm.
4. Calculated Increase:
   a. Expected increase based on growth in previous 3 mo. = 2 × 6 = 12 cm.
   b. Contributed by unfolding of isthmus: 14.6 cm.
   c. Total increase = *26.6* cm.

The calculated and experimental figures check remarkably well.

This evidence does not prove that the isthmus actually unfolds in the manner described, because we have no way of knowing what changes would occur if the isthmus did not unfold. The sudden spurt in growth rate might be due to growth stimuli (hormones and distention). However, the evidence is certainly suggestive that unfolding has occurred, particularly when considered together with the more conclusive evidence for a similar process in the monkey.

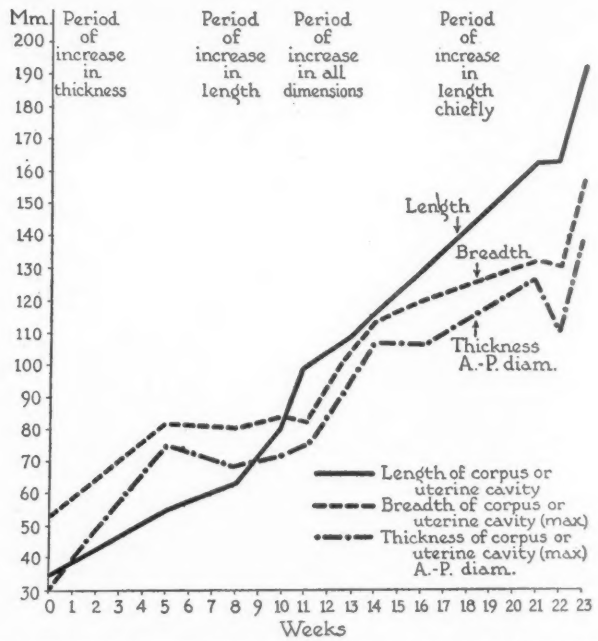

Fig. 6.—Curves constructed from Stieve's data (Table I), which compare favorably with the data in Table II.

3. *Is it reasonable to believe that the entire so-called lower uterine segment which exists prior to and during labor can be the result of growth of the isthmus uteri?* In fact, the answer to this question was the chief reason why we measured 73 frozen sections of the uterus in the various stages of pregnancy. To obtain the data shown in Table II we selected those frozen sections which appeared to be most free from uterine pathology. This, of course, decreased the number of sections available. Measurements of excised specimens found in the literature were also measured and studied.

In answering this question it was necessary to make two assumptions. First, the retraction ring or a definite thickening of the wall marks the junction of the upper and lower segments. Second, if the lower segment develops from the isthmus, then the longitudinal muscle fibers of the

TABLE II. RESULTS OF CERTAIN MEASUREMENTS MADE ON HUMAN FROZEN SECTIONS * 66 SECTIONS WERE MALIGNANT 45 COMPLETELY

TABLE II. RESULTS OF CERTAIN MEASUREMENTS MADE ON HUMAN FROZEN SECTIONS.* 66 SECTIONS WERE MEASURED AS COMPLETELY AS THE SECTION PERMITTED

STAGE OF PREGNANCY	NO. OF CASES	EXT. FUND. TO E. O. CM.	INT. LENG. OF CAVITY C CM.	LENG. OF CERVIX CM.	THICK. OF FUND. WALL CM.	LOWER EDGE OF PLACENTA TO I.O. CM.	DIAM. OF PLACENTA CM.	CIRCUM. OF CAVITY CM. D	RATIO OF LENGTH TO CIRCUM. OF CAVITY C-D
1 month	6	9.0	4.6	3.6	0.8	—	—	10.4	44.2
2 months	3	11.3	6.3	4.0	1.0	—	—	15.3	44.2
3 months	6	12.5	8.2	4.1	1.0	1.3	—	20.8	40.0
4 months	8	15.4	10.4	4.3	0.7	2.8	10.5	26.6	39.1
5 months	4	21.6	17.1	3.6	0.7	6.8	13.1	44.0	38.8
6 months	3	24.5	20.9	3.0	0.7	9.0	—	53.5	39.0
7 months	5	25.4	21.7	3.4	0.5	11.1	16.0	55.3	39.2
8 months	4	26.5	23.5	2.4	0.6	13.2	15.4	60.5	38.8
8 months (early labor)	3	27.3	24.2	1.3	0.8	11.9	17.2	61.9	39.0
9 months	5	27.7	24.6	2.7	0.7	15.2	17.5	65.2	38.0
Labor, 1st Stage	8	28.1	25.3	2.0	0.7	13.0	17.2	66.7	38.0
Labor, 2nd Stage						E. O.			
Bumm and Blumreich		--	26.9	2.0	—	7.0	—	69.6	38.6 Early
Hillis		34.5	30.5	3.2	0.8	15.0	18.0	71.2	42.8 Early
Braune		27.4	26.5	0.1	0.8	15.3	18.0	65.4	40.5 Early
Canton		25.3	22.9	0.6	1.8	11.6	15.0	55.7	41.1 Vertex deep
Barbour and Webster		24.0	22.9	0.1	1.1	8.4	—	55.9	40.9 Vertex at vulva
Couvelaire		22.8	22.0	0.3	0.5	11.7	14.0	51.5	42.7 Vertex at vulva
Canton		17.2	15.6	0.3	1.3	—	10.1	41.6	37.5 Vertex at vulva
Labor, 3rd Stage		Total Int. Leng.						Total Int. Circum.	
Placenta not separated	4	18.5						46.3	40.0
Placenta separated	4	17.7						40.1	44.1
1st day, post partum	4	18.0						41.2	43.6
1-5 days, post partum	6	13.7						30.5	45.0
Nonpregnant Nulli	6	6.8	3.1	Is. 0.5 Cx. 2.7	0.5			6.3	50.0
Nonpregnant Multi	4	7.8	3.7	Is. 0.7 Cx. 2.7	0.7			7.4	50.0

*Only those which involved no pathology of uterus or pelvis are included. The sections are sagittal.

TABLE IIA. RATE OF CHANGE IN LENGTH AND SAGITTAL CIRCUMFERENCE OF UTERINE CAVITY

MONTH	LENGTH CM.	SAG. CIRCUM. CM.	A. INCREASE IN LENGTH CM.	B. INCREASE IN CIRCUM. CM.	B. - A. SLOPE OF CURVE	
0	3.4	6.8	—	—	—	
0 to 1st	4.6	10.4	1.2	3.6	3.0	
1st to 2nd	6.2	15.3	1.6	4.9	3.1	2.95
2nd to 3rd	8.2	20.8	2.0	5.5	2.75	2.87
3rd to 4th	10.4	26.6	2.2	5.8	2.64	
4th to 5th	17.1	44.0	6.7	17.4	2.6	
5th to 6th	20.9	53.5	3.8	9.5	2.5	2.56
6th to 7th	21.7	55.3	0.8	1.8	2.3	2.54
7th to 8th	23.5	60.5	1.8	5.2	3.0	
8th to 9th	24.6	65.0	1.1	4.5	4.0	Relation of length to circumference is close to that of a circle
9 mo., 1st stage of labor	25.3	66.7	0.7	1.5	2.1	

isthmus during pregnancy should increase in length to the same extent as those of the corpus.

The actual measurements reveal that the musculature of the corpus elongates in its sagittal circumference from 6.9 to 8.0 times during pregnancy. The musculature of the isthmus elongates in its sagittal internal surface from 7.3 to 13 times. If one chooses the average circumference of the nongravid corpus (6.9 cm.) and chooses 1.0 cm. as the length of one side of the nongravid isthmus, then the corpus increases in length 7.4 times and the isthmus 7.3 times.

CALCULATIONS REGARDING THE SAGITTAL GROWTH OF THE ISTHMUS AND CORPUS UTERI IN PREGNANCY

A. Average internal sagittal circumference of uterine cavity at term (Table II).
Average of 9 mo. term and 9 mo. first stage 65.8 cm.

B. Average internal sagittal circumference contributed by lower uterine segment:
1. Length of lower uterine segment, cesarean section, Marshal and others 7-10 cm.;
2. Average length of lower uterine segment, frozen section (Table III) 7.3 cm.
$(2 \times 7.3) = 14.6$ cm.

C. Average sagittal circumference contributed by corpus (A-B) 51.2 cm.

D. Average sagittal circumference of uterine cavity in
Nulliparous (Table II) 6.3
Multiparous (Table II) 7.4
Average 6.9 cm.

E. Increase in sagittal circumference of corpus in pregnancy:
1. $51.2 \div 6.3$ (Nulli) $= 8.0$ times.
2. $51.2 \div 7.4$ (Multi) $= 6.86$ times.
3. $51.2 \div 6.9$ (Ave.) $= 7.4$ times.
4. Using only 9 mo. term or 9 mo., first stage measurements, or both (Table III), to conform with "A" above the average length of one wall of the lower uterine segment is 9.1, or 11.1 (average with cervix) minus 2.5 (average length of cervix), which equals 9.1 cm., or $2 \times 9.1 = 18.2$.
$65.8 - 18.2 = 47.6$ cm., for the sagittal circumference of corpus.

47.6 ÷ 6.9 (average circumference, nongravid, uterine cavity) = 6.9 times.

F. Increase in sagittal length of corpus in pregnancy ranges from 6.9 to 8.0 times.

G. The increase of the length of the isthmus in pregnancy depends on the length accepted for the nongravid isthmus.

1. The maximum length of one wall is 1.0 cm.;
2. The minimum length of one wall is 0.45 cm.;
3. The average length of one wall is 0.7 cm., or

Average total length is 2 × 0.7 = 1.4 cm., on the basis of maximum length; the total length is 2.0 cm.

a. 14.6 (see B 2 above) ÷ 2.0 = 7.3 times.
b. 14.6 ÷ 0.9 = 16.2 times.
c. 14.6 ÷ 1.4 = 10.4 times.
d. 18.2 (see E 4 above) ÷ 1.4 = 13.0 times.
e. 18.2 (see E 4 above) ÷ 2.0 = 9.1 times.

H. Increase in sagittal length of isthmus in pregnancy ranges from 7.3 to 13.0 times, omitting the minimum figure for the length of the isthmus.

The correlation between the extent of growth in length of the isthmus and corpus is striking. This is particularly true when one recalls that before the physiologic retraction ring becomes definitely evident, some increase in the length of the fibers of the isthmus and decrease in the length of the fibers of the corpus may have occurred. Keeping this in mind, it is reasonable to believe that all of the so-called lower segment, exclusive of that contributed by the true cervix in labor, develops from the isthmus. The only way to settle the question would be to place some nonabsorbable material at the level of the retraction ring in labor, and then determine its position in the fully involuted uterus.

III. CERTAIN OBSERVATIONS RESULTING FROM A STUDY OF FROZEN SECTIONS OF THE HUMAN UTERUS

In the preceding study it was necessary to identify the "retraction ring" or the junction of the isthmus and corpus as accurately as possible. This caused us to make measurements which are of interest in relation to the lower segment cesarean operation and to the problem of constriction ring dystocia.

The Relation of the Lower Edge of the Placenta to the Retraction Ring and the Obstetric Internal Os.—In the monkey the lower edge of the placenta, as a rule, was a good indication of the site of the physiologic retraction ring in labor. This was not found to be so true in the human being.

In the term uterus (9 mo.), the lower edge of the placenta was located on the average 15.2 cm. circumferentially above the obstetric internal os (Table II). The retraction ring was located on the average 9.1 cm. circumferentially above the obstetric internal os. Or, the lower edge of the placenta was located on the average 3.1 cm. above the retraction ring. In the ninth month, first stage specimens, the lower edge of the placenta was located on the average 2.1 cm. (13.0 – 9.1 = 2.1 cm.) above the retraction ring.

The Relation of the Retraction Ring to the Peritoneal Bladder Fold.—The average circumferential distance from the bladder fold to the external cervical os was 5.9 cm. (Table III). The average circum-

TABLE III. AN ANALYSIS OF THOSE CASES SHOWING DEFINITE RETRACTION RINGS OR THICKENING AT JUNCTION OF UPPER AND LOWER SEGMENTS (HUMAN FROZEN SECTIONS)§

OUR CASE	LOCATION OF P.R.R. OR RING		P.P.R.* TO E. O.		BLADDER** FOLD TO E. O.	FUNDUS† TO R.R.		R.R.‡ TO LEVEL OF SYMPHYSIS VERTICAL		R.R. CORRESPONDS TO FETAL DEPRESSION	AVERAGE LENGTH OF CERVICAL LIPS	STAGE OF LABOR	NATURE OF RING
	A.	P.	A.	P.		A.	P.	A.	P.				
			I.O.	I.O.									
16	×	×	9.3	11.2	7.0 I.O.	28.7	18.3	0	8.5	---	?	9, Term	Thickening
17	0	×	12.0	--	3.5 I.O.	30.2	--	--	--	---	?	9, Term	Thickening
19	×	0	12.4	--	6.0	20.9	--	--	--	---	2.5	9, Term	Thickening
21a	×	×	14.2	10.6	5.2	23.4	23.7	+11.8	--	---	--	9, Term	Thickening
24	0	×	9.5	11.1	9.8	—	18.1	+ 1.0	+ 8.1	Yes	2.1	8, Term I	Definite
31	×	×	10.7	13.7	7.5	26.9	23.4	0	+ 7.0	Yes	2.6	9, Term I	Definite
33	×	×	12.0	15.6	?	21.5	14.9	+ 0.8	+10.0	Yes	2.4	9, Term I	Definite
40	×	×	9.5	7.9	2.2	26.3	28.8	+ 9.6	+ 9.2	Leg down	0	9, Term I	Definite
41	×	×	6.4	11.9	6.8	36.8	18.5	+ 3.0	10.6	Yes	2.0	Term, II	Definite
42	×	×	10.8	10.6	7.6	20.7	23.7	+ 3.0	+ 9.7	Yes	0.1	Term, II	Definite
43	×	×	8.4	7.6	4.1	23.1	18.8	+ 4.0	+ 9.0	Yes	0.1	Term, II	Definite
44	×	×	8.5	5.8	6.8	24.1	18.6	+ 2.0	+ 8.2	Yes	0.7	Term, II	Definite
46	×	×	6.4	4.3	4.8	17.3	17.5	4.2	7.6	Yes	--	Term, II	Definite
47	×	×	3.0	4.3	?	20.2	14.7	+ 2.2	+ 6.8	Yes	0.6	Term, II	Definite
48	×	×	8.3	5.3	3.0	16.3	14.7	+ 0.7	- 0.1	---	2.4	Term, III	Definite
53	×	×	9.0	6.6	?	11.3	11.2	--	--	---	?	Term, III	Definite
55	×	×	7.1	3.0	6.4	13.9	14.2	- 2.7	- 0.9	---	1.3	P.P.	Definite
56	×	×	9.0	4.8	7.3	12.3	20.7	+ 4.4	+ 5.2	---	2.0	P.P.	Definite
Ave.			9.2	8.4	5.9			+ 3.7			1.5		
Ave.			8.8		Ave. length of l.u.s. = 8.8 - 1.5 (cervix) = 7.3 cm.								

*Hillis case not included.

**The measurements represent the distance measured circumferentially along the internal curvature of the uterus.

†Ant. P.R.R. is above level of symphysis in all cases including those from 8 months to end of second stage. Total cases, 18; average vertical distance above level of symphysis is 4.0 cm.; range = +0.3 to +11.8 cm.

‡Note that on the average the bladder fold of the peritoneum is 3.3 cm. below the P.R.R. This checks well with Marshall (1, p. 45). The bladder fold is below the P.R.R., but the very firm attachment of peritoneum to uterus is generally above (2 to 3 cm.) the P.R.R.

§P.R.R., Physiologic retraction ring; A., anterior; P., posterior; l.u.s., lower uterine segment.

ferential distance from the retraction ring to the external os was 9.2 (Table II). Thus, the bladder fold was found on the average to be 3.3 cm. below the retraction ring. This checks well with the measurements of Marshall (ref. 26, p. 45) made during cesarean section. He finds that the bladder fold is usually located below the physiologic retraction ring, but the firm attachment of the peritoneum to the uterus is usually located 2 to 3 cm. above the ring.

The Variability in the Extent of the Retraction Ring in the Absence of Disproportion.—A study of all the frozen sections in the literature reveals that the extent of the retraction ring varies considerably, as was observed in the monkey. In Fig. 8 is shown four frozen sections illustrating the variability. Some rings are strictly located, as in Fig. 8, *1*, to the posterior wall of the uterus and would probably be overlooked at a cesarean operation. A few completely surround the uterus.

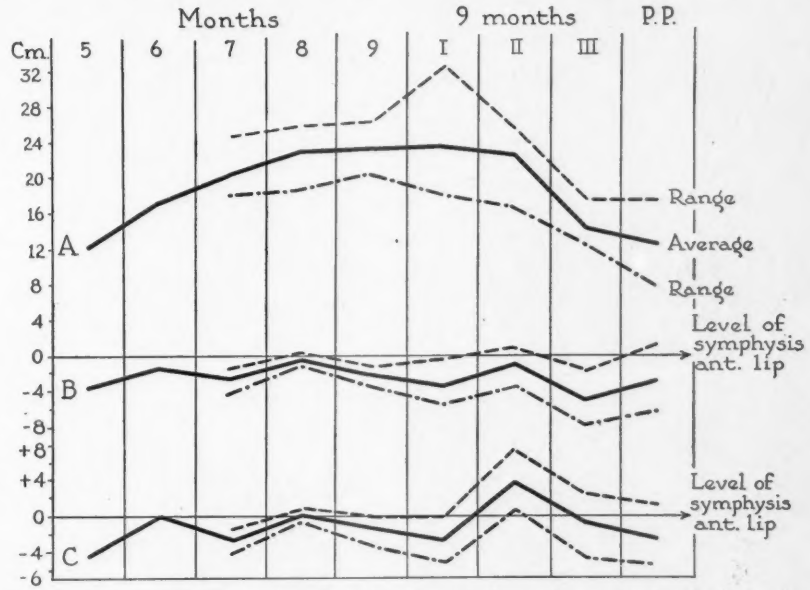

Fig. 7.—Graph showing the position of the fundus and the anterior and posterior cervical lips during pregnancy and labor.

Of 73 specimens studied, a definite physiologic retraction ring, or a "retraction ring," was found in only 38, or 52 per cent. A definite projecting ring was present in 14, or only 19 per cent. A definite thickening was found in 24, or 33 per cent. By "definite thickening" is meant a place regarding which everyone would agree that the corpus becomes thicker. In other instances the thickening is so gradual (Fig. 8, *4*) that no definite place could be labeled as a physiologic retraction ring. Other data of interest regarding retraction rings are recorded in Table IV.

The Relation of the Physiologic Retraction Ring, or Retraction Ring, to the Level of the Superior Border of the Symphysis.—All the rings in the frozen sections studied by us from eight months to the end of the

second stage of labor were located above the horizontal plane of the superior border of the symphysis. In 13 cases in which the ring was located anteriorly, the average vertical distance from the symphysis to the ring was 3.7 cm., the range being –2.7 (one case) to +11.8 cm. (Table III).

The Thickness of the Uterine Musculature or Wall at Various Levels Before and During Labor.—The thickness of the uterine wall was measured at the points indicated in Table V. An analysis of the data reveals

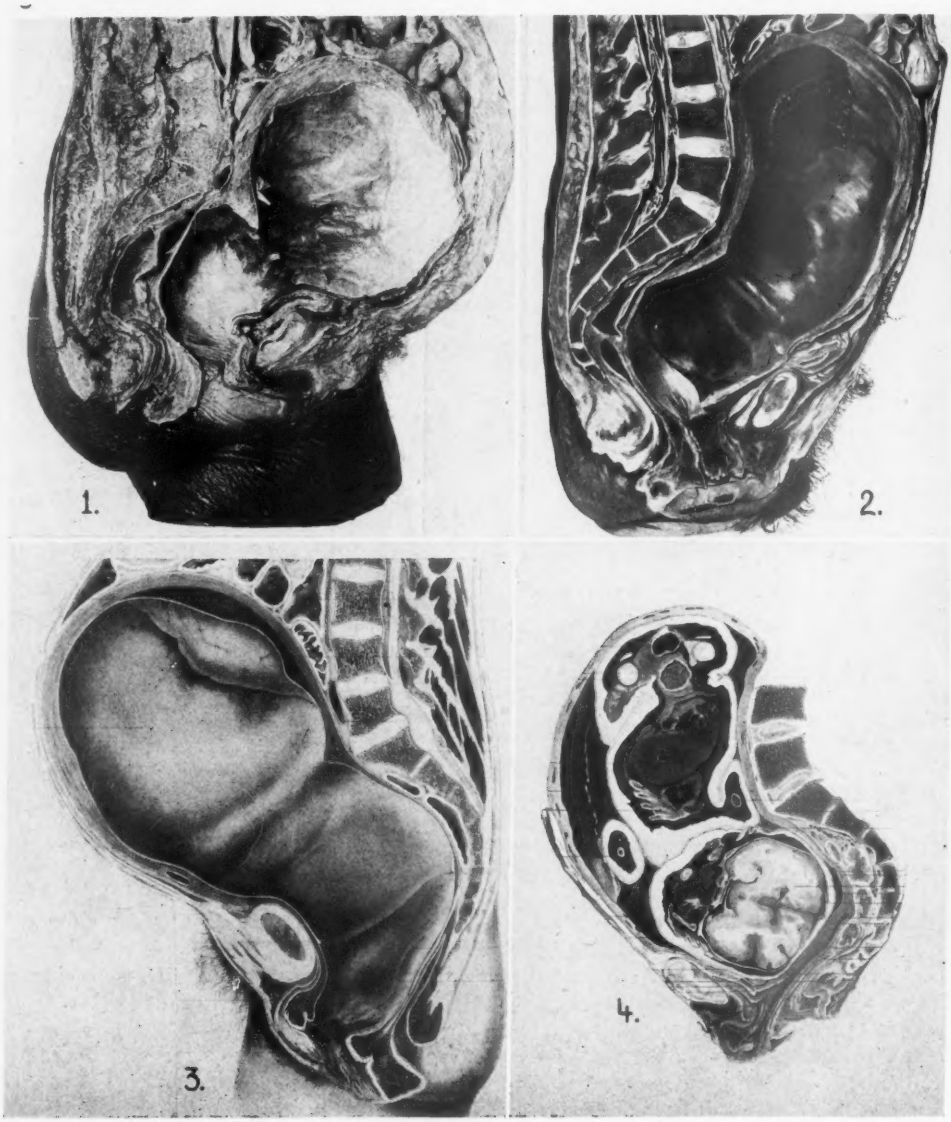

Fig. 8.—Frozen sections illustrating the variability in retraction rings in the absence of disproportion. Section *1* is from Canton; Section *2* is from Canton; Section *3* is from Braune; and Section *4* is from Barbour. Barbour's section was in the first stage. The others are second stage.

TABLE IV. SUMMARY OF DEFINITE RETRACTION OR "CONSTRICTION RINGS"

	PER CENT
I. Of 73 cases studied, physiological retraction ring, or a definite retraction ring was present in 38, or	52.0
Definite ring, present in 14 cases	19.2
Thickening only, present in 24 cases	33.0
II. Of 48 cases during labor and up to fourth day post partum: Ring present in 14 cases.	29.9
III. Of 14 definite rings:	
3 occurred in first stage of 17 cases	17.6
1 occurred in Braxton Hicks' Version of 3 cases	33.3
6 occurred in second stage of 8 cases	75.0
2 occurred in third stage of 8 cases	25.0
2 occurred in post partum of 11 cases	18.2

(The unpublished case of Dr. Hillis is included.) Of the 10 rings found in the first and second stages, 9, or 90 per cent, correspond to fetal depressions. The other one occurred in a Braxton Hicks' version.

that on the average during the first stage of labor the length of the lower segment increases only slightly, if any. The lower segment, however, becomes definitely thinner. This must be due chiefly to an horizontal increase in the length of the circular musculature. During the second stage, the average length of the lower segment definitely decreases, i.e., from 9.1 to 6.6 cm.

On reviewing and measuring the thickness of the uterine wall in labor, one is amazed by the variability particularly in the retraction of the corpus, as revealed by the frozen section method.

Changes in the Position and Length of the Cervical Lips.—In the monkey in labor, it was found that the cervical lips during the second stage of labor (frozen sections) retracted about the presenting part to the level, or usually above the level of the superior border of the symphysis.[118] The data from the frozen sections of the human uterus are presented in Table VI. Unfortunately in many cases the section did not pass through the cervical canal. For this reason some of the sections are of no value for detailed mensuration.

The data obtained (Table VI) indicate that from the eighth month of pregnancy to the beginning of the second stage of labor the cervical lips tend to sink in relation to the symphysis. During the second stage, they are definitely elevated and even the anterior lip in some instances (2 of 7) may rise slightly above the symphysis. This occurs in the absence of known disproportion. This is particularly true of the posterior lip (see Fig. 7).

The excursion of the cervical lips during labor in the living subject is best studied by placing radiopaque clips on the cervical lips. This method, which is being employed by Caldwell and Stillman,[8] should yield precise information. Their preliminary results indicate that the cervical lips in the human being during the second stage of labor retract to a higher level in labor than is generally believed.

The frozen sections reveal that the extent to which the cervical lip is retracted into the lower segment in labor is subject to wide variation. In some cases only a lip 2 mm. long hangs below the level of the fornix; in other cases as much as 3.4 cm. In the latter case it appears as if no retraction of the cervix into the lower segment has occurred.

TABLE V. THICKNESS OF WALL OF UTERUS AT VARIOUS LEVELS BEFORE AND DURING LABOR (HUMAN FROZEN SECTIONS)‡

STAGE	NO. OF CASES	MIDWAY BETWEEN CERVIX AND P.R.R. OR THICKENING		JUNCTION OF U.U.S. AND L.U.S.		MIDCORPUS		TOP OF FUNDUS	AVERAGE L.U.S. WITHOUT CERVIX CM.	
		ANT. MM.	POST. MM.	ANT. MM.	POST. MM.	ANT. MM.	POST. MM.			
9 mo.	6	5.1	5.7	7.0	7.8	7.0	7.4	7.0	9.1	Ave.
Term		2.5-7.0	2.0-10.0	4.5-8.5	5.5-11.0	3.5-10.0	5.0- 9.0	5.0- 8.0	6.8-11.7	Range
8 mo.	3	2.0	4.4	4.3	5.8	7.0	7.8	7.8		Ave.
1st		1.5-2.5	3.5- 6.0	4.0-5.0	5.0- 7.0	5.5- 9.5	5.5-10.0	5.5-10.0		Range
9 mo.	9	3.2	4.2	5.6	5.6	7.4	6.2†	7.4	9.3	Ave.
1st		1.0-5.0	2.5- 6.5	4.5-7.0	4.0- 8.0	6.0-11.0	2.5- 8.0	2.5-23.0	7.9-13.2	Range
9 mo.	7	3.5	4.6	6.0	14.5*	10.3	10.7	10.3	6.6	Ave.
2nd		2.5-6.0	3.0- 8.0	4.0-8.0	5.0-36.0*	7.0-18.0	6.5-22.0*	5.0-15.0	3.0- 9.9	Range

*Due to a very thick R.R. and retraction of posterior uterine wall; may have been a Bandl's ring, though there was no disproportion and the l.u.s. was not thin, but retracted markedly longitudinally.

†Due to excessive thinning anteriorly and thickening posteriorly in one specimen by Leopold.

Note: During the first stage, the average length of the l.u.s. increases only slightly, if any; however, the l.u.s. becomes definitely thinner, which must be due to distention or an horizontal increase in length. During the second stage, the average length of the l.u.s. decreases definitely and the corpus becomes definitely thicker.

‡U.U.S., upper uterine segment; L.U.S., lower uterine segment.

TABLE VI. SHOWING LEVEL OF CERVICAL LIPS AND EXTERNAL HEIGHT OF FUNDUS IN RELATION TO THE HORIZONTAL PLANE OF THE UPPER BORDER OF THE SYMPHYSIS (HUMAN FROZEN SECTIONS)

STAGE	NO. OF CASES	CERVICAL LIPS AS RELATED TO LEVEL OF SYMPHYSIS*				HEIGHT OF FUNDUS ABOVE PLANE OF SYMPHYSIS	
		ANTERIOR		POSTERIOR			
		AVE.	RANGE	AVE.	RANGE	AVE.	RANGE
7 mo.	4	−2.8	−1.6 to −4.1	−2.8	−1.5 to −4.1	20.3	18.1 to 24.8
8 mo.	4	−0.6	−1.0 to +0.2	0	−0.6 to +0.7	22.9	18.9 to 25.9
9 mo.	4	−2.2	−1.5 to −3.7	−1.2	0 to −3.7	23.1	20.3 to 26.7
8 mo. I	4	−0.8	−2.0 to 0	+0.6	−1.0 to +2.0	23.2	19.4 to 25.8
9 mo. I	6	−3.8	−5.7 to −0.6	−2.8	−5.0 to 0	23.8	17.9 to 32.5
9 mo. II	7	−1.3	−3.8 to +0.7	+3.8	+0.3 to +7.4	22.4	16.7 to 25.5
9 mo. III	3	−5.0	−1.4 to −8.0	−0.5	−4.6 to +2.5	14.1	12.6 to 17.6
Post partum	8	−3.0	−6.5 to +1.4	−2.3	−5.6 to +1.4	12.7	7.8 to 17.6

*(−) = below level of symphysis; (+) = above; (0) = at level.

Note: According to the data, from eight months to, and including, the first stage of labor the cervical lips tend to sink in the pelvis, but during the second stage they are definitely elevated to sink again at the third stage.

SUMMARY

1. A structural, as well as a comparative anatomic and physiologic background, exists for the mode of travel of the wave of uterine contraction in the primate uterus.

2. The evidence pertaining to the growth and unfolding or inclusion of the isthmus uteri into the general uterine cavity to form the so-called lower uterine segment may be summarized as follows:

a. Histologically the isthmus uteri increases from 2 to 3 times in length during the first three months of pregnancy and then unfolds and is included in the general uterine cavity. No evidence contrary to this observation in the human being could be found. Histologic and gross anatomic observations in the monkey lend substantial confirmation.

b. The muscular fasciculi of the isthmus in pregnancy assume a more longitudinal or steeper course, but the architecture of the true cervix and corpus is not significantly modified. There is no contrary evidence; yet, one should like to have confirmation of Goerttler's observations.

c. The membranes are relatively loosely attached to the lower segment and the mucosa of the lower segment differs histologically from that of the upper segment. This evidence is not substantial in that no definite line of demarcation between the two segments can be detected.

d. The changes in the form of the uterus in pregnancy are compatible with and suggest that some event happens between the third and fourth month of pregnancy which contributes (a) to a definite change in the breadth and thickness of the uterine cavity, (b) to a greater increase in vertical length in relation to the increase in the sagittal circumference of the cavity, and (c) to a rather sudden increase in the average distance of the lower edge of the placenta from the internal os (Table II).

e. Using the "retraction ring" as the point of junction between the isthmus and corpus in late pregnancy and labor, it was found that the muscular fasciculi undergo approximately equal increases in longitudinal length in pregnancy. Or, it was found reasonable to conclude that an isthmus only 1 cm. long in the nongravid state may hypertrophy until it is 7 to 10 cm. in length at term.

f. To obtain direct evidence, it would seem to be necessary to place some nonabsorbable material in the musculature at the site of the retraction ring in labor and then determine the site of the material in the fully involuted uterus.

3. Data obtained from the mensuration of frozen sections of the human uterus have been analyzed in relation to the location and variability of the physiologic retraction ring and the position and dilatation of the cervical lip during labor.

NOTE: It should be stated that all the data on which the averaged values in the tables are based cannot be published in a short article. Dr. D. N. Danforth and I hope to publish a monograph including photographs of all frozen sections and the data upon which the averaged values are based.

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SOME ASPECTS OF EARLY HUMAN DEVELOPMENT*

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TO FURTHER a comprehensive study of the factors of human reproduction, we have started, at the Free Hospital for Women, the systematic collection of human ova. Among several hundred eggs obtained from follicles, we have recovered two in the first maturation division. We have also isolated one perfect unfertilized tubal ovum. From uteri removed at operation we have recovered twelve very young human conceptuses with which this report deals. Together with the tubal ovum, these specimens have been added to the collection of primate ova in the Department of Embryology of the Carnegie Institution of Washington.† Here they are utilized by Doctors George W. Corner, George L. Streeter, and Chester Heuser in their study of human embryology. To these investigators and their associates we owe the careful sectioning and photographing of the specimens. We are also grateful for their help in the basic interpretations on which this paper rests.

The heavy clinical load of the Free Hospital for Women has been admirably adapted to our purpose. Patients seen in the Out-Patient Department who require surgical relief for conditions not immediately harmful must await hospitalization usually for several months. From women who are put on the list for operation by the examining surgeons in the Out-Patient Department we select those to whom the following statements apply:

1. They are incapacitated by symptoms caused by gross uterine displacement or minor uterine pathology, which can best be relieved by hysterectomy.
2. Their menstrual habit is such as to indicate probable regular ovulation.
3. They are living with their husbands and are willing and intelligent enough to cooperate.

The selected patients are asked to report each menstrual period during the months of waiting for admission and to record the dates of coitus during the cycle in which operation is to take place. In some of the more recent cases urine for assay of hormones has also been collected prior to operation.

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*Read at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

This study has been aided by grants from the Carnegie Corporation of New York, the William F. Milton Fund of Harvard University, and the Committee for Research in Problems of Sex, National Research Council.

†The accession numbers of the Carnegie Institution of Washington are used to designate the specimens discussed in this report.

MATERIAL

So far 61 women from 26 to 44 years of age have helped in this study. They had had from 2 to 15 pregnancies each. There had been an average of 7.3 previous pregnancies in those cases in which normal ova were obtained, an average of 6.8 pregnancies each in cases in which abnormal ova were recovered, and an average of 4.8 previous pregnancies per patient in the 48 cases in which young embryos were not found.

Of the 12 conceptuses recovered in the course of this investigation, 7 are considered to be normal. One lacks the embryo, so it may be said to be congenitally destined for abortion, and four others are probably so. The only endometrial deviation from normal was seen in the one case, Be-7771, which is minus the embryo. This ovum is situated in a polypoid bit of mucosa (Fig. 3).

Two of the normal ova, Si-7699 and Al-7700, were reported briefly to the American Association of Anatomists in 1939, and the material pertaining to Al-7700 was published as an abstract in the *Anatomical Record*.[1] Later both these specimens were described in detail in the *Contributions to Embryology* of the Carnegie Institution of Washington.[2] Five of the normal embryos (including the two mentioned above) and four of the pathologic ones were discussed before the American Society for Experimental Pathology in April, 1942.[3] In a paper read before the American Association of Anatomists, also in the spring of 1942, Re-7950 and Si-7699 were compared with regard to their respective implantation sites.[4]

The present paper utilizes three additional ova: one abnormal, Sm-8000, and two normal, Mu-8020 (Fig. 1) and Wi-8004 (Fig. 2). The latter two specimens, estimated to be between 7 and 8, and between 9 and 10 days old, respectively, are, as far as we know, the youngest human embryos ever seen and are now reported for the first time. The next three normal ova in the order of age, dated 11.5, 12.0, and 12.5 days old (mean values), are represented in Figs. 3, 4, and 5, respectively.

The structural details of the specimens not already described will in time appear in the *Contributions to Embryology* of the Carnegie Institution of Washington. We merely wish to mention a few of the clinical lessons derived from our studies thus far.

The following subjects are considered:

1. The probable time of ovulation as evidenced by embryo age and endometrial histology.
2. The time of nidation.
3. The location of embedment.
4. The frequency of abnormal ova.

1. THE PROBABLE TIME OF OVULATION AS EVIDENCED BY EMBRYO AGE AND ENDOMETRIAL HISTOLOGY

The ages of 11 embryos have been tentatively estimated by Drs. Streeter and Heuser by comparing their development with that of monkey conceptuses of known ovulation ages. The twelfth specimen, Be-7771, is undatable, since it lacks an embryo.

How long a time elapses between ovulation and fertilization? It seems likely that for prolonged orderly development to occur after the

first maturation division, the regulating influence of the male pronucleus must be added within a short time, for it has been found, both in human beings and in lower mammals, that, although segmentation may occur in vivo in unfertilized ova,[5-8] atresia soon follows. We have noted abnormal cleavage in human ovarian eggs during the first twenty-four hours of culture in vitro. On the basis of present evidence, it seems likely that no more than one day intervenes between ovulation and fertilization. This time interval may be taken then as the possible error in age of embryo when it is considered the same as ovulatory age. The ovulation ages recorded in Table I range from between 7 and 8 to between 16 and 17 days or, expressed in terms of mean values, from 7.5 to 16.5 days.

TABLE I. TIME OF OVULATION IN CYCLE AS INDICATED BY AGE OF EMBRYO AND CONDITION OF ENDOMETRIUM ON DAY OF OPERATION

CASE*	MEAN ESTIMATED AGE OF OVUM (DAYS)	ESTIMATED INTERVAL BETWEEN OPERATION AND NEXT CATAMENIA AS JUDGED BY CONDITION OF ENDOMETRIUM (DAYS)	INTERVAL BETWEEN ESTIMATED OVULATION AND ANTICIPATED MENSTRUATION (DAYS)	DAY OF CYCLE ON WHICH OPERATION TOOK PLACE	ESTIMATED PREOVULATORY INTERVAL (DAYS)
Mu—8020	7.5	6	13.5	24	16.5
Wi—8004	9.5	2	11.5	25	15.5
Si—7699	11.5	3	14.5	25	13.5
Tr—7770	11.5?	3	14.5?	31	19.5?
Er—7850	11.5?	3	14.5?	31	19.5?
Sm—8000	11.5?	3	14.5?	28	16.5?
Re—7950	12.0	5	17.0	26	14.0
Al—7700	12.5	2	14.5	29	16,5
Br—7800	13.0?	2	15.0?	32	19.0?
Ru—7801	13.5	2	15.5	28	14.5
Bu—7802	16.5	0	16.5	33	16.5

*Ovum Be-No. 7771 is not included in this table since, due to the absence of the embryo, its age could not be estimated.

?Indicates abnormal specimen whose age could not be estimated as accurately as in the cases of normal ova.

Except in the immediate proximity to the embryo, the endometrium, barring unusually persistent edema, seems unaffected by the pregnancy. The third column in Table I shows the estimated time in days needed in each case after the day of operation for those histologic changes to ensue which normally take place in the endometrium before menstruation is begun in a fully developed predecidua. If this stated number of days in each case is added to the age of conceptus, we derive an idea of the time interval by which ovulation preceded anticipated menstruation. This time interval ranges approximately from 11.5 to 17.0 days (Column 4). If now the estimated mean age of the conceptus is subtracted from the cycle day on which operation was performed (Column 5), we see that ovulation took place from days 13.5 to 19.5 of the cycle (Column 6). The cases in which the interval is more than 16.5 days are, however, those of abnormal ova in which the assigned ages may be less accurate than in the normal ones.

The impression might be gained from these figures that ovulation occurs in the middle of the cycle and that it is as accurately placed by reckoning from the onset of the last menstrual flow as from the next

anticipated period. For other reasons, we believe this is not so. Two of our cases are better controlled than the others and give more dependable information on this subject. In each of these there was but a single insemination. Ovulation could not have preceded coitus by many hours. In Mu-8020, coitus took place late on the sixteenth day of the cycle. At laparotomy performed on the twenty-fourth day, the endometrium showed that there were still six days to go before a menstrual predecidua would probably be developed; i.e., it is apparent that, in the absence of pregnancy, menstruation would have occurred on the thirtieth day of the cycle. The conceptus obtained is considered to be seven to eight days old. Hence ovulation in this well-controlled case took place

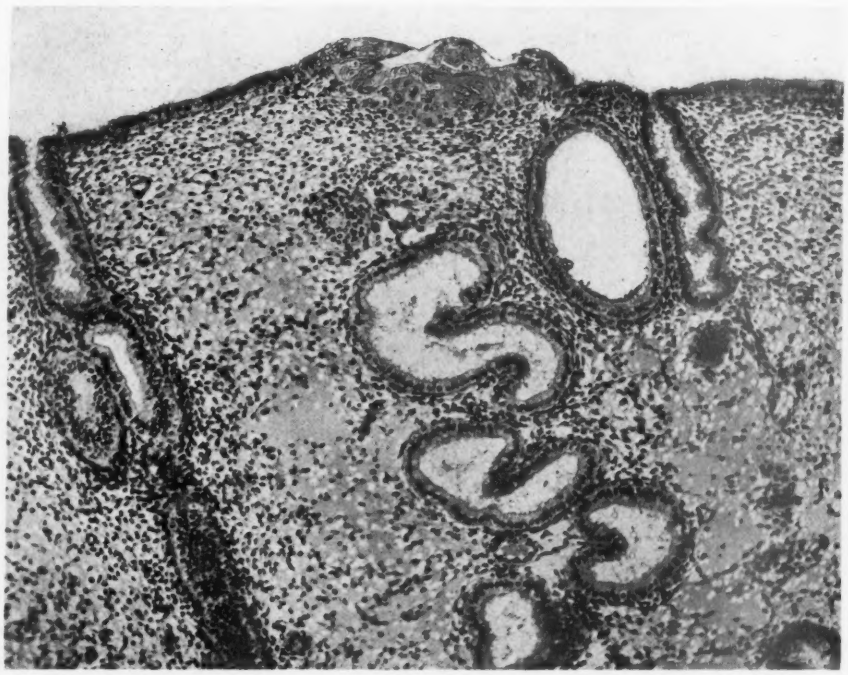

Fig. 1.—Mu-8020. A 7.5-day human ovum implanted on physiologically edematous twenty-two-day secretory endometrium. At its site of attachment to the endometrium, the ovum shows a thick proliferation of its trophoblast which is mostly of the syncytial type. The embryo is represented by the rounded mass of cells just above the trophoblastic mass and beneath the thin membranous portion of the collapsed blastocyst wall. The surface epithelium of the endometrium is defective at the site of implantation but is undergoing proliferative repair at the margin of the defect. Hematoxylin and eosin. ×100. Figures are arranged in the order of ascending age of the ova.

fourteen to thirteen days [(8 to 7) + 6] before anticipated menstruation, and between days sixteen and seventeen of the cycle. In Case Al-7700, operation was performed on the twenty-ninth day, but the endometrium showed that a menstrual predecidua would not have developed until two days later. The conceptus is considered to be twelve to thirteen days old. Ovulation therefore is judged to have occurred fifteen to fourteen days [(13 to 12) + 2] before anticipated menstruation, and between days sixteen and seventeen of the cycle.

Hence it appears in these two cases that ovulation takes place about fourteen days before menstruation. In a twenty-seven-day cycle (with

menstruation on the twenty-eighth day) ovulation takes place not only about the fourteenth day (14 ± 2) before the beginning of catamenia, but also in the middle of the cycle. When the cycle is longer than twenty-seven days, as in the two cases mentioned above, ovulation still takes place about the fourteenth day before the first day of flow, but in these cases not in the middle of the cycle. The postovulatory period approaches a constant; the preovulatory phase is of variable length.

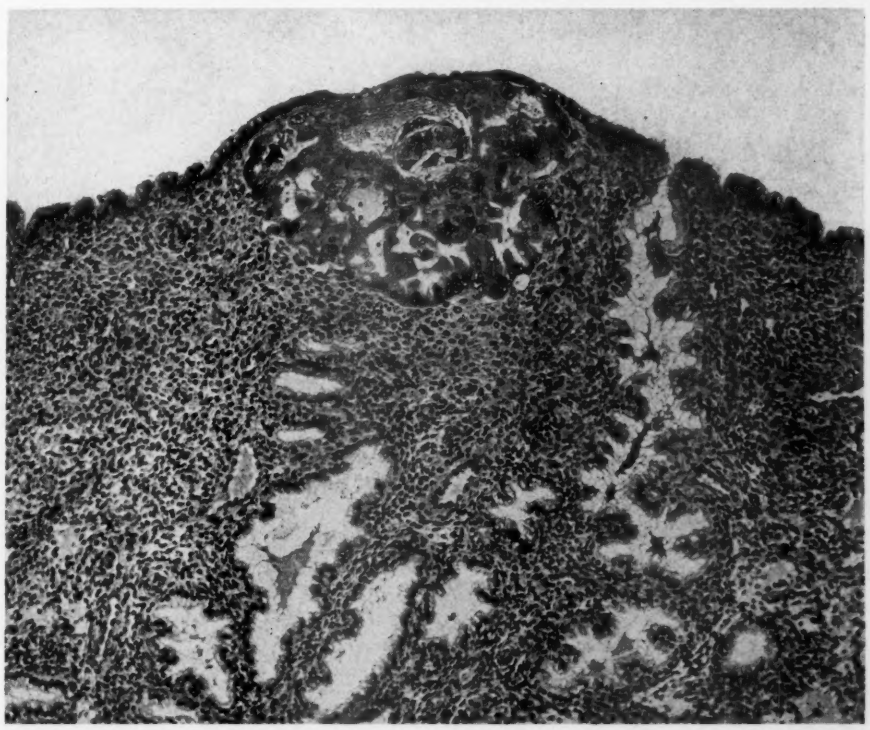

Fig. 2.—Wi-8004. A 9.5-day human ovum implanted within the surface of twenty-six-day secretory endometrium. The defective endometrial epithelium has been partially repaired and is in the process of closing the defect created by the implanting ovum. The thick syncytiotrophoblastic plate now contains numerous coalescing lacunae for the reception of maternal blood. Some syncytiotrophoblast has formed on the abembryonic wall of the ovum, due to contact with endometrium. The embryo, a bilaminar germ disk with beginning amniotic cavity below, is composed of a thick plate of ectoderm and a thin plate of primitive entoderm. The cavity within the ovum (future chorionic cavity) contains artifactual blood. Hematoxylin and eosin. ×100.

This is a conclusion which we draw not from the small number of conceptuses which we have obtained, but from much more extensive studies of the endometrium as it reflects changing endocrine activity of the ovary. The values in Column 4 of Table I do not vary significantly from the figure 14 ± 2. Difficult as it is to determine just how long progestin has been acting on an endometrium, it is even more difficult to determine the exact age of an embryo. The fact that the figures in Column 4 of Table I were derived from estimates in regard to both these factors may account for the minor deviations noted.

2. THE TIME OF NIDATION

Heuser and Streeter[9] have shown in the monkey that when contact is made with the endometrium, the trophoblastic tissue of the tiny

vesicle consists only of the thin shell of the blastocyst itself and a small grouping of cells which, together with the fewer and more primitive "formative" cells, make up the embryonic pole. It is beneath this area that nidation occurs. The trophoblastic nuclei of the auxiliary cells promptly become distinguishable from the formative cells, multiply, and form an invasive syncytium. We have as yet seen no free human blastocyst. In our youngest ovum, Mu-8020 (Fig. 1), syncytium and signs of early lacunae are easily discernible. The number and size of the formative cells in the embryonic disk, and the integrity of the

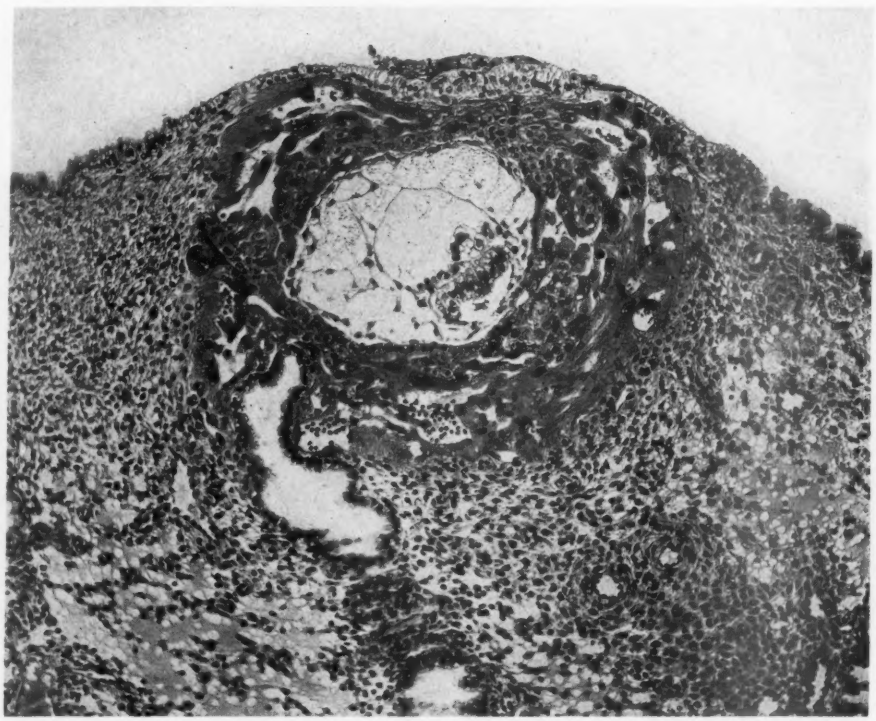

Fig. 3.—Si-7699. An 11.5-day human ovum embedded in twenty-five-day secretory endometrium. The endometrial epithelium has completely regenerated over the ovum, although some coagulum from a near-by defect is apparent on the surface. Within the outer syncytiotrophoblast is an intercommunicating lacunar network containing some maternal blood. The inner cytotrophoblastic layer of the chorion is beginning to develop. The bilaminar germ disk (embryo) is seen toward "4 o'clock," with its amniotic cavity below and its exocoelomic cavity above. There is a suggestion of early decidua about the ovum and the moderately prominent spiral arteriole, with surrounding predecidua in the lower right corner. Hematoxylin and eosin. ×100.

amniotic cavity, together with the mass of the whole ovum and the degree of development of the trophoblast, indicate that the conceptus is seven to eight days old. Furthermore it should be noted that the single coitus in this case preceded operation by 7.5 days. Embedment has barely begun, yet the trophoblastic growth must have taken a considerable time, possibly as long as 48 hours, to be accomplished. This would place nidation five to six days after ovulation; i.e., on the nineteenth to the twentieth day of a twenty-seven-day cycle.

Our next specimen in the order of age is that of Wi-8004 (Fig. 2). This was almost completely submerged in the endometrium, yet its histology indicates that it is only nine to ten days old. Judging from

the histologic relationship of endometrium to trophoblast, nidation must have been started at least three days before; i.e., between the sixth and seventh postovulatory days, or between the twentieth and twenty-first days of a twenty-seven-day cycle. Study of these two conceptuses indicates that contact with the endometrium may be established as early as the fifth or sixth postovulatory day.

If we consider one of the older ova, Al-7700 (Fig. 5), which is regarded as being twelve to thirteen days old, we see it is still not completely covered, but the advanced relationship between the trophoblast

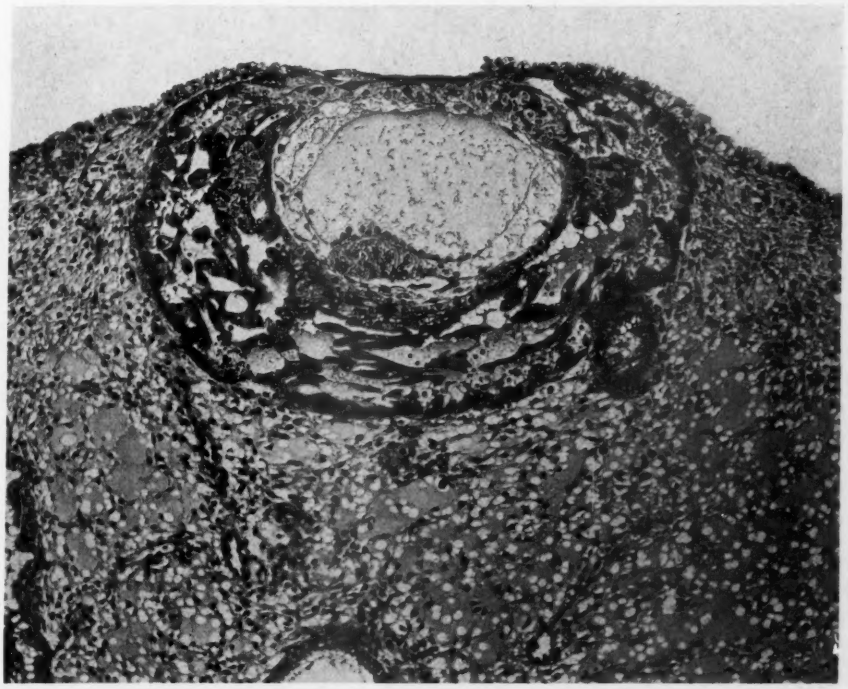

Fig. 4.—Re-7950. A twelve-day human ovum embedded in twenty-three-day secretory endometrium. The latter is at its peak of physiologic edema. The defect in the surface of the endometrium has not yet been completely repaired. The structure of the ovum is essentially the same as that of Si-7699 (Fig. 3), except that the lacunar network within the syncytiotrophoblast is more prominent. The exocoelomic cavity is a little larger and the embryo is located in the more usual position; i.e., directly at the embryonic pole instead of to one side, as in the former specimen. Hematoxylin and eosin. ×100.

and the endometrium, as well as between the lacunae and the maternal vessels, indicates an attachment of more than three days, perhaps as many as five days. Thus nidation in this case might have occurred as late as the eighth day after ovulation; i.e., on the twenty-second day of a twenty-seven-day cycle.

Comparison of the estimated duration of embedment with the degree of endometrial development at the time of operation leads us to think either that nidation may occur on an endometrium exhibiting a variable degree of what has long been called "progestational" or "functional" activity, or else that the degree of ovular development may vary considerably at the moment nidation is started.* For example,

*That the former is more likely has already been suggested in a previous communication.[4]

comparison of ova Re-7950 and Al-7700 (Figs. 4 and 5) will show that, although the conceptuses are of about the same age and have apparently been on the endometrium the same period of time, the phase of endometrial development varies by as much as three days.

Even more striking is the discordance between Wi-8004 (Fig. 2) and Re-7950 (Fig. 4). Although the former is considered to be *two to three days younger* than the latter, the endometrium surrounding it is dated as *three days older* than that on which the much more advanced ovum is embedded.

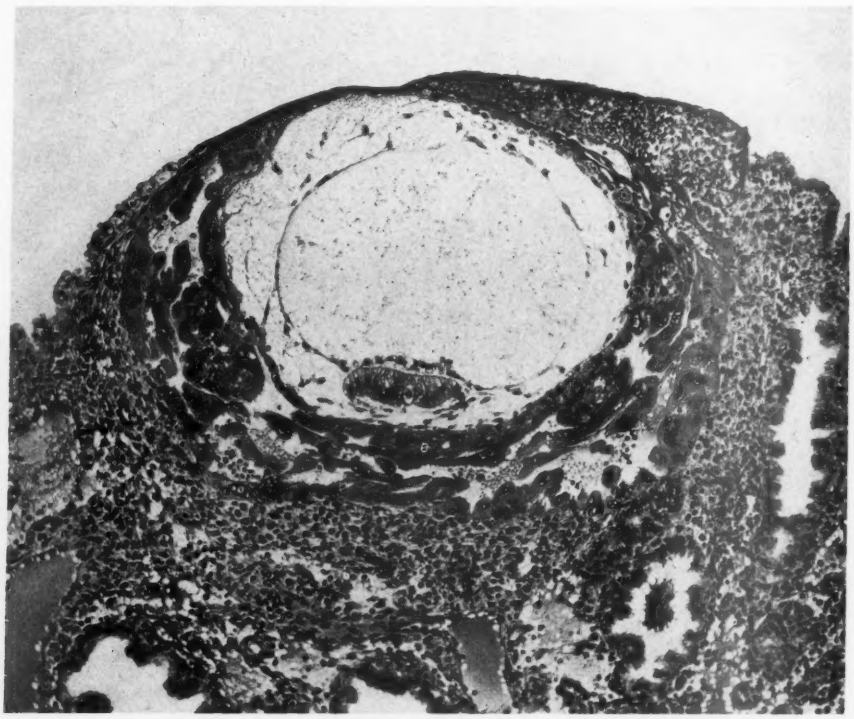

Fig. 5.—Al-7700. A 12.5-day human ovum embedded in twenty-six-day secretory endometrium. This specimen is less deeply implanted than the 9.5, 11.5,- and twelve-day stages. The overlying endometrium is either very deficient or necrotic. The trophoblastic lacunae, constituting the future intervillous space of the placenta, are more prominent and contain more maternal blood than in the younger ova. The primordia of chorionic villi are seen in the four masses of proliferating cytotrophoblast located at "3," "4," "6," and "8 o'clock" respectively. The embryo is essentially the same as in the twelve-day specimen. Early decidual reaction about the ovum is slightly more prominent than in the 11.5-day specimen. Vascular response to the ovum is marked in the surrounding endometrium and appears in the form of large, dilated, thin-walled sinusoids. Endometrial glands are of actively secretory type. Hematoxylin and eosin. ×100.

Ova Mu-8020 and Si-7699 (Figs. 1 and 3) are more nearly comparable. The former is *three* to *four* days younger than the latter, and the corresponding endometrium is in a phase dated *three* days earlier. Both these ova started embedment on a similar phase of endometrial development.

Not only may the endometrium vary at the time of nidation, but, as has already been stated, the conceptuses may vary in age from a minimum of five days to a maximum of perhaps even eight days at the time they start to invade the endometrium.

The earliest likely attachment we have seen takes place when the endometrium is in the primary edematous stage with beginning glandular secretion (Mu-8020). The latest nidation of which we have evidence, in the three cases cited, apparently occurred only one to three days later (Al-7700). During this phase there is still much edema, but, toward the end of it, also swelling of the stroma cells around the hypertrophied spiral arterioles and just beneath the binding epithelium. In other words, nidation seems to take place on endometrium which is from nine to six days shy of a complete menstrual predecidua; i.e., between days nineteen and twenty-two of a twenty-seven-day cycle.

TABLE II. LOCATION OF IMPLANTATION SITES OF NORMAL AND ABNORMAL EMBRYOS

CASE	MEAN ESTIMATED AGE OF OVUM (DAYS)	OVARY CONTAINING ACTIVE CORPUS LUTEUM	LOCATION OF IMPLANTATION SITE		CONDITION OF OVUM
			LATERAL PLACEMENT	ANTERIOR OR POSTERIOR WALL	
Mu—8020	7.5	Right	Nearer left	Posterior	Normal
Wi—8004	9.5	Right	Right cornu	Posterior	Normal
Si—7699	11.5	Left	Equidistant	Posterior	Normal
Re—7950	12.0	Right	Nearer right	Posterior	Normal
Al—7700	12.5	Right	Left	Posterior	Normal
Ru—7801	13.5	Right	Nearer right	Posterior	Normal
Bu—7802	16.5	Right	Left	Posterior	Normal
Er—7850	11.5?	Left	Nearer right	Anterior	Abnormal
Sm—8000	11.5?	Left	Left	Anterior	Abnormal
Tr—7770	11.5?	Right	Right	Anterior	Abnormal
Br—7800	13.0?	Right	Right	Anterior	Abnormal
Be—7771	—*	Left	—	Anterior	Abnormal

*This specimen could not be dated due to the absence of the embryo.

3. THE LOCATION OF EMBEDMENT

Table II shows the location of the implantation sites in the several uteri, and, for comparison, the respective ovaries containing the active corpora lutea. Surprisingly, all the normal conceptuses were found implanted on the posterior wall of the uterus, whereas all those considered abnormal were located on the anterior wall. This may be a spurious relationship, but it is interesting, at least for the time being. There seems to be no correlation between lateral placement and the ovary of origin. Apparently, as in the monkey, the free blastocyst is passively moved about in the uterine cavity until it is able to attach itself. The duration of its stay in the uterus, and hence the age at which it enters, cannot be stated conclusively until after the recovery of free blastocysts, a difficult accomplishment.

4. THE FREQUENCY OF ABNORMAL OVA

Four of our twelve specimens are judged to have defective auxiliary structures; a fifth ovum, Be-7771, is certainly abnormal for it lacks the embryo. Hertig and Edmonds[10] have already demonstrated that the absence of all or most of the embryo is the commonest single finding in completed spontaneous abortions.

Five (42 per cent), then, of the 12 embryos are considered abnormal, thus giving evidence of inevitable abortion. If 42 per cent of pregnancies are aborted, many must be lost before the diagnosis of pregnancy is made, for it is computed that only about 8 per cent of diagnosed pregnancies are spontaneously aborted.[11] If this figure of 8

per cent approaches accuracy, we must assume that additions to our collection will contain a smaller proportion of abnormal embryos, or that subsequent growth in those which appear abnormal would re-establish normal structure.

SUMMARY

1. Seven very young normal human conceptuses and five abnormal ones have been recovered from twelve of 60 excised uteri. One of the normal specimens, Mu-8020, estimated to be seven to eight days old (mean: 7.5) is, as far as we know, the youngest human embryo yet reported. The others range in age up to sixteen to seventeen days (mean: 16.5). By comparison of the age of the embryo with the associated endometrial histology, it is apparent that ovulation in two well-controlled cases occurred about fourteen (fifteen to thirteen) days before the anticipated dates of menstruation.

2. From a consideration of three ova estimated to be 7.5, 9.5, and 12.5 days old (mean values), we learn that nidation takes place at a variable age of the embryo, perhaps from the fifth to the eighth day of age, and on an endometrium which may vary in phase from the nineteenth to the twenty-second day of a twenty-seven-day cycle (catamenia on the twenty-eighth day).

3. The seven normal conceptuses were found on the posterior wall of the uterus, and the five abnormal ones on the anterior wall, probably a correlation which will not hold when more specimens are collected. The locus of nidation is not affected by the side on which the egg enters the uterus.

4. Five (42 per cent) of our twelve young embryos are so pathologic as to indicate probable early abortion. This figure (42 per cent) is of course higher than the percentage of abortions among diagnosed pregnancies. It is conceivable that more cases will show a lower proportion of defective ova. It seems likely from these findings, however, that either many pregnancies abort before recognition, during apparent normal menstruation, or that cytologic improvement takes place in some formerly abnormal conceptuses.

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DISCUSSION

DR. WILLIAM E. STUDDIFORD, New York, N. Y.—The results which have been reported have been reached by a correlation of clinical facts with histologic study. This has resulted in the full utilization of a very limited supply of material. Such material might be more rapidly gathered if organized search for such specimens, under the direction of Dr. Rock, was carried out in institutions similar to the Free Hospital for Women in Brookline. While considered at Bellevue Hospital, the idea was abandoned because of the lack of opportunity for the prolonged study of the patient while on a preoperative waiting list. Without the accumulation of the necessary clinical facts, the mere collection of the specimens would not be of any great value.

A more rapid accumulation of such early embryos might serve to reinforce or modify certain of the observations made on the basis of the present series. The estimation of the probable time of ovulation coincides fairly closely with the present clinical beliefs. Might not study of augmented material reveal occasional wider variations in this time? The question of duration of the functional capacity of spermatozoa in humans can only be answered in further studies. Certain experimental studies in animals suggest that their function shows a sharp decrease after twenty-four hours.

Most remarkable is the occurrence of 42 per cent abnormal embryos, apparently doomed to abortion, a figure much higher than the accepted abortion rate. With the accumulation of a larger series, is it not probable that this percentage will decrease? No more understandable is the preference of the abnormal ovum for the anterior wall of the uterus. Here it would seem certain that a larger series would prove such a conclusion to be in error.

THE EFFECT OF PROGESTERONE IN ADOLESCENT GIRLS AND YOUNG WOMEN WITH FUNCTIONAL UTERINE BLEEDING*

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THE exact etiology of abnormal bleeding from the uterus, excluding that due to neoplasms, continues to be obscure. The increased knowledge of the reproductive cycle and our appreciation of the various means by which uterine bleeding can be produced experimentally in those mammals that menstruate, make it quite obvious that previous explanations, such as hyperestrinism, failure of ovulation, and ovarian deficiency do not fully explain all types of excessive and prolonged bleeding. Even the terms menorrhagia and metrorrhagia have lost their supposed differential significance because of the insistence of some gynecologists that bleeding due to breakdown of a nonprogestational endometrium is not menstruation. Failure of ovulation may, of course, result in hyperestrinism but the disturbances which result may be due to a deficiency of progesterone rather than to hyperestrinism. The only salient point seems to be that whenever the ovary is unable for any reason whatever to undergo periodically a cycle manifested by growth and rupture of a follicle, with formation of a normal corpus luteum, followed by normal involution of that corpus luteum, abnormal bleeding may occur. This, however, does not mean that abnormal bleeding always occurs whenever the ovary is unable to undergo an ovulatory cycle. Many fairly regular periods doubtless occur during adolescence, lactation, and the climacteric in the absence of ovulation without the appearance of excessive or prolonged bleeding. In fact, estrogen-deprivation of proper magnitude practically always results in menstruation. The complicating factor is progesterone. Progesterone-deprivation of proper magnitude also results in menstruation, and furthermore, even small amounts given for only a few days may result in progesterone-deprivation bleeding regardless of whether the endometrium shows progestational changes or not.

If it be true that prolonged and excessive bleeding, occurring especially in adolescent girls and young women, is associated with failure of ovulation, one might expect beneficial results from the use of pro-

*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

gesterone. If the bleeding be due to hyperestrinism, progesterone should result in a decrease in the hyperestrinism, even though the amount of estrogen being produced remains unaltered. Also after a course of treatment with adequate amounts the endometrium should break down and be shed as during menstruation following an ovulatory cycle. This by itself should be beneficial, since it should result in the destruction of a hyperplastic endometrium. Progesterone might also be expected to have an effect on the pituitary, perhaps decreasing the output of follicle-stimulating hormone. Follicle growth is ordinarily relatively suppressed when corpus luteum activity is greatest, probably because of inhibition of the pituitary, and hence the administration of progesterone might be expected to produce an effect on the pituitary similar to that brought about by activity of the corpus luteum itself. With these thoughts in mind we have treated a group of patients with progesterone and anhydrohydroxy progesterone.*

Progesterone has already been used by numerous investigators for the treatment of functional uterine bleeding, although the results have not been consistent (see Hamblen, 1942). Increased bleeding has been sometimes observed (Hamblen, 1936) whereas improvement has also been observed (Clauberg, 1932; Knab, 1933; Lauterwein, 1940; Wenner, 1940; Wiesbaden, 1941; Wilson, 1936).

The general plan of treatment was to withhold therapy until bleeding had been in progress for two weeks or more. Progesterone was then given daily by intramuscular injection for a period of four to eight days. In the earlier observations only 2 mg. were given daily but, as the hormone became more readily available, the dose was increased to either 5 or 10 mg. daily. Anhydrohydroxy progesterone (ethinyl testosterone, pregneninolone) has been given orally to several patients. The amount given has varied from 180 mg. to 600 mg., but in general the total dose was given over a period of from four to eight days. In those cases in which there was anemia, some form of iron, usually ferrous sulfate, was given. The basal metabolic rate was determined in the majority of the cases at some time during the period of observation. Desiccated thyroid, however, was not given initially to any of the patients until after the effect of progesterone had been observed. In some cases abnormal bleeding occurred while thyroid was being given and in them the thyroid was continued at the same level while the effect of progesterone was being observed.

The detailed menstrual records and the pertinent data concerning therapy are shown in the charts. The duration of bleeding is shown by the broad black lines or squares. The height of the black band does not accurately indicate the amount of bleeding, except that the narrower bands and smaller squares indicate bleeding described by the subject as being scant. The duration of medication is indicated by the

*The progesterone and anhydrohydroxy progesterone used in this study were furnished by The Schering Corporation, Bloomfield, N. J.

short line just above the indicated amount. All amounts over 100 mg. represent anhydrohydroxy progesterone given orally, and all amounts under 100 mg. represent progesterone given intramuscularly. When the indicated amount was between 20 and 40 mg., the daily amount was 5 mg., and when the total amount was more than 40 mg. and less than 100 mg., the daily dose was 10 mg. In the few instances in which less than 20 mg. were given, the daily dose was usually 2.0 mg.

From an inspection of the charts, it is evident that in many instances essentially normal menstrual periods occurred for several months after a single course of injections. In other cases the bleeding ceased either

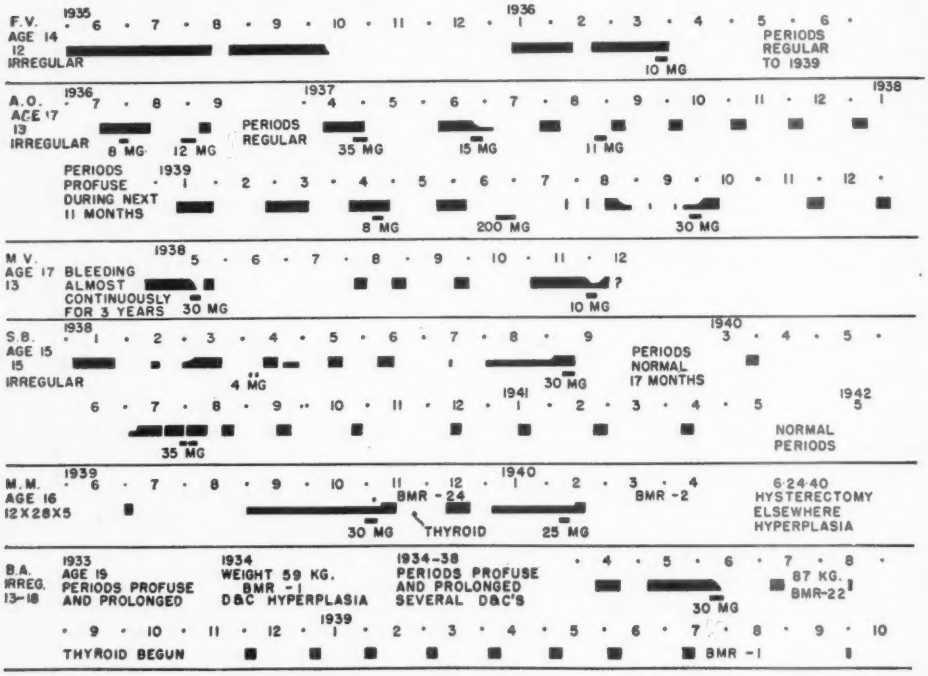

Fig. 1.

Figs. 1 to 5.—Detailed chronologic record of the periods of bleeding and the therapy utilized.

during the injections or within a few days after the injections, but prolonged bleeding recurred again within a few weeks. In still other cases the bleeding was interrupted only to be followed by amenorrhea for many weeks. When the larger doses of progesterone or of anhydrohydroxy progesterone were given, there was usually an increase in bleeding, beginning about forty-eight hours after the discontinuation of the hormone and lasting for about five or six days. In most instances this progesterone-deprivation bleeding was not excessive, but occasionally the bleeding was considerably more than the subject ordinarily experienced during a menstrual period.

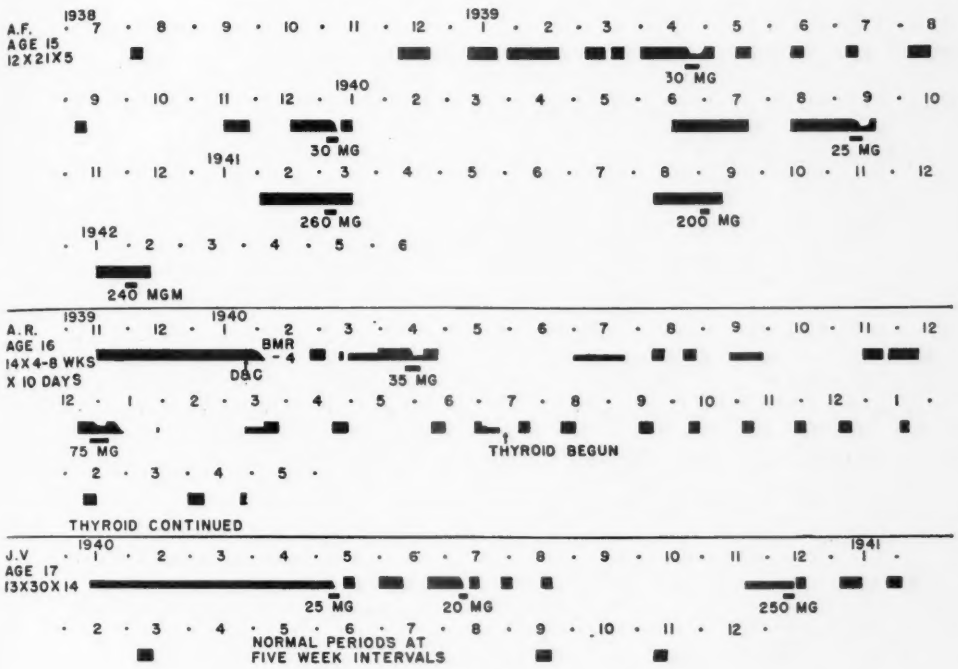
A.F.
AGE 15
12X21X5
1938
1939
1940
1941
1942
30 MG
30 MG
25 MG
260 MG
200 MG
240 MGM
A.R.
AGE 16
14X4-8 WKS
X 10 DAYS
BMR
-4
D&C
35 MG
75 MG
THYROID BEGUN
THYROID CONTINUED
J.V
AGE 17
13X30X14
25 MG
20 MG
250 MG
NORMAL PERIODS AT
FIVE WEEK INTERVALS

Fig. 2.

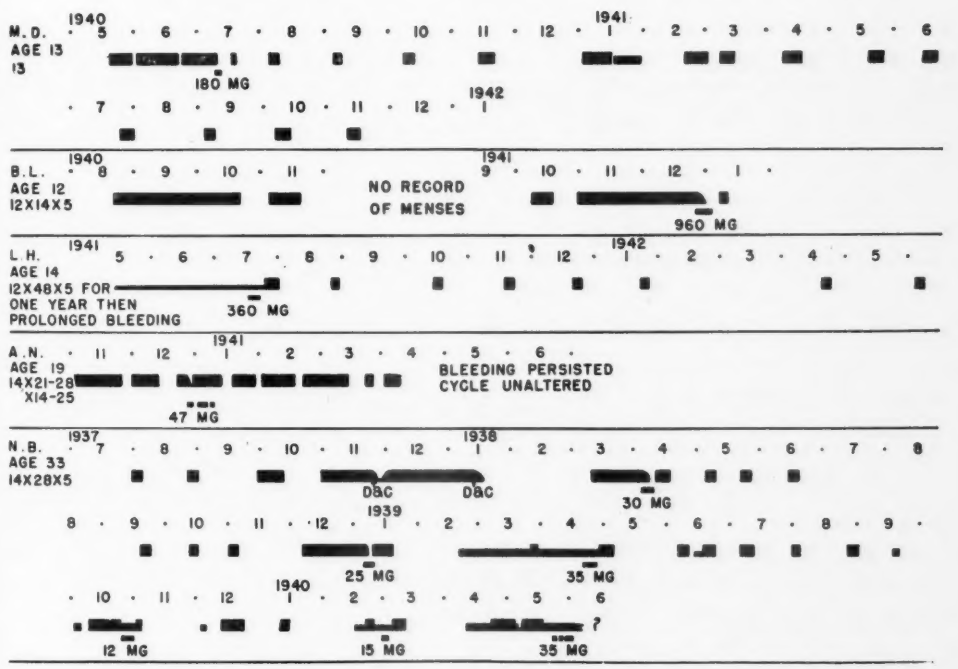
M.D.
AGE 13
13
180 MG
B.L.
AGE 12
12X14X5
NO RECORD
OF MENSES
960 MG
L.H.
AGE 14
12X48X5 FOR
ONE YEAR THEN
PROLONGED BLEEDING
360 MG
A.N.
AGE 19
14X21-28
X14-25
47 MG
BLEEDING PERSISTED
CYCLE UNALTERED
N.B.
AGE 33
14X28X5
D&C
D&C
30 MG
25 MG
35 MG
12 MG
15 MG
35 MG

Fig. 3.

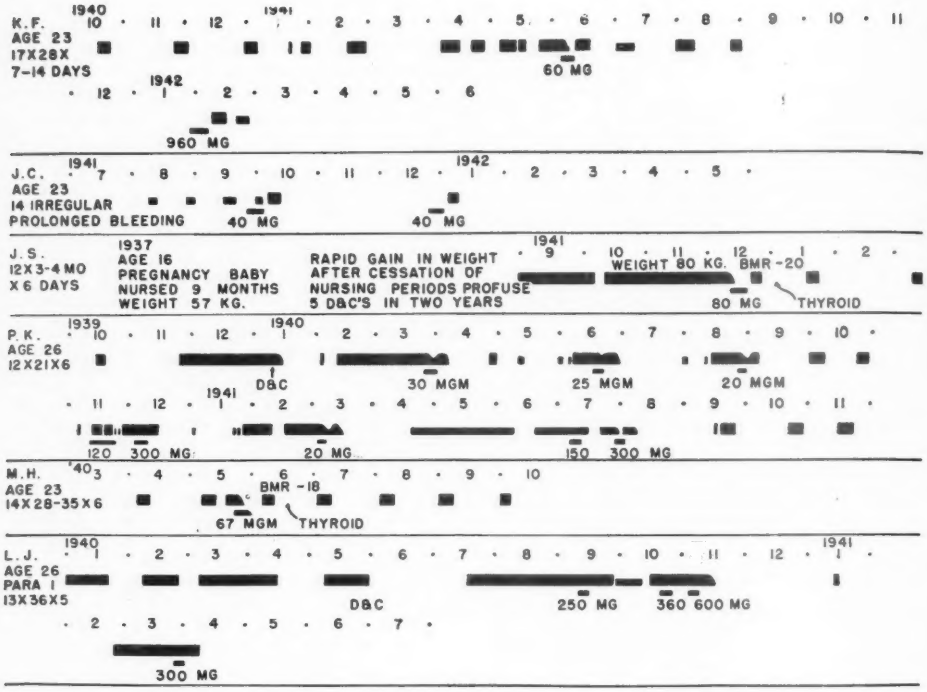
K.F.
AGE 23
17X28X
7-14 DAYS
60 MG
960 MG
J.C.
AGE 23
14 IRREGULAR
PROLONGED BLEEDING
40 MG
40 MG
J.S.
12X3-4 MO
X 6 DAYS
AGE 16
PREGNANCY BABY
NURSED 9 MONTHS
WEIGHT 57 KG.
RAPID GAIN IN WEIGHT
AFTER CESSATION OF
NURSING PERIODS PROFUSE
5 D&C'S IN TWO YEARS
WEIGHT 80 KG. BMR -20
80 MG
THYROID
P.K.
AGE 26
12X21X6
D&C
30 MGM
25 MGM
20 MGM
120
300 MG
20 MG
150
300 MG
M.H.
AGE 23
14X28-35X6
BMR -18
67 MGM
THYROID
L.J.
AGE 26
PARA 1
13X36X5
D&C
250 MG
360 600 MG
300 MG

Fig. 4.

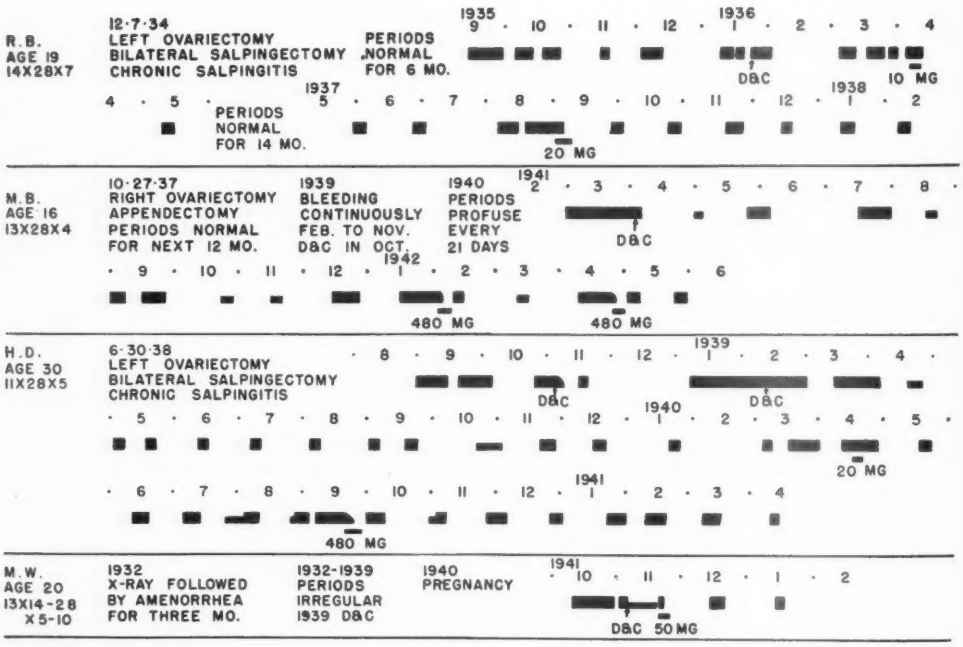
R.B.
AGE 19
14X28X7
12-7-34
LEFT OVARIECTOMY
BILATERAL SALPINGECTOMY
CHRONIC SALPINGITIS
PERIODS
NORMAL
FOR 6 MO.
D&C
10 MG
PERIODS
NORMAL
FOR 14 MO.
20 MG
M.B.
AGE 16
13X28X4
10-27-37
RIGHT OVARIECTOMY
APPENDECTOMY
PERIODS NORMAL
FOR NEXT 12 MO.
1939
BLEEDING
CONTINUOUSLY
FEB. TO NOV.
D&C IN OCT.
1940
PERIODS
PROFUSE
EVERY
21 DAYS
D&C
480 MG
480 MG
H.D.
AGE 30
11X28X5
6-30-38
LEFT OVARIECTOMY
BILATERAL SALPINGECTOMY
CHRONIC SALPINGITIS
D&C
D&C
20 MG
480 MG
M.W.
AGE 20
13X14-28
X 5-10
1932
X-RAY FOLLOWED
BY AMENORRHEA
FOR THREE MO.
1932-1939
PERIODS
IRREGULAR
1939 D&C
1940
PREGNANCY
D&C 50 MG

Fig. 5.

The data presented in the charts have been studied to ascertain, if possible, how much effect the progesterone has really had on the course of the disease in these patients. The duration of bleeding before therapy has been contrasted with the duration of bleeding after therapy. For this study five consecutive periods have been considered. The first period (days 1 to 30) is one of thirty days in which no therapy was given. In many instances the amount of bleeding in this period was negligible because of the frequent occurrence of amenorrhea prior to abnormal bleeding. The second period of thirty days (days 31 to 60) followed the first period and was terminated on the last day of therapy. These two periods in reality cover the period of sixty days immediately preceding the last day of therapy, and any bleeding occurring during these periods represents bleeding unaltered by therapy, except as it may have been influenced by the short period of therapy. The third period (days 61 to 70) is of only ten days. Since progesterone-deprivation frequently is followed by a menstrual period, it seemed necessary to separate any bleeding which may have occurred for this reason from bleeding which occurred subsequently. The fourth period (days 71 to 100) covers the first thirty days after the time when progesterone-deprivation bleeding should have been completed and the fifth and final period (days 101 to 130) covers the next thirty days. By grouping the data in this manner it is possible to compare the duration of bleeding in two consecutive periods of thirty days each before (and including) therapy with the duration of bleeding in two consecutive periods of thirty days each after the cessation of therapy, the periods before and after therapy being separated by a period of ten days in which bleeding may have occurred as a result of withdrawal of the hormone.

The data have been further rearranged into three groups. In the first group (Table I), the observations are listed in which the menstrual periods were essentially normal for four months or more after

TABLE I. SUMMARY OF OBSERVATIONS IN WHICH THERAPY WAS FOLLOWED BY NORMAL MENSES FOR FOUR OR MORE MONTHS

SUBJECT	BLEEDING DURING DAYS						NORMAL PERIODS MONTHS	RECURRENCE
	1-30	31-60	PROGESTERONE* MG.	61-70	71-100	101-130		
F. V.	20	30	10	0	5	5	36	No
A. O.	6	14	8	10	5	6	8	Yes
	0	22	15	6	10	5	6	
	14	10	30	9	0	8	6+	
S. B.	13	30	30	0	5	5	17	
	5	28	35	5	6	7	24	
A. F.	15	28	30	7	7	8	4	Yes
J. V.	0	23	250	4	10	7	12	
M. D.	22	27	180	3	5	4	6	
L. H.	30	30	360	9	3	0	11	
R. B.	8	20	10	0	6	6	14	Yes
	5	23	20	0	6	6	7	
N. B.	30	30	35	8	1	15	4	Yes
H. D.	9	20	20	7	5	8	4	Yes
	15	23	480	8	8	9	6	
QM. H.	6	15	67	5	7	7	4	
Average	12.4	23.3		5.0	5.6	6.6		

*Progesterone or anhydrohydroxy progesterone, therapy ending sixtieth day (see text).

the use of progesterone. In the second group (Table II), the observations are listed in which there was a recurrence of abnormal bleeding in less than four months, and in the third group (Table III) are listed the observations in which amenorrhea followed either immediately or after two or three menstrual periods. In addition to the cases given are eight observations in which the follow-up has been for less than four months. In each of these untabulated cases there was cessation of bleeding but the subsequent course was either unknown or the therapy had been too recent for adequate observation.

TABLE II. SUMMARY OF OBSERVATIONS IN WHICH THERAPY WAS FOLLOWED BY RECURRENCE OF ABNORMAL BLEEDING WITHIN FOUR MONTHS

SUBJECT	BLEEDING DURING DAYS						RECURRENCE AFTER WEEKS
	1-30	31-60	PROGESTERONE* MG.	61-70	71-100	101-130	
A. O.	5	20	35	0	0	24	6
	21	17	8	8	13	2	4
J. V.	30	27	25	5	11	22	6
P. K.	20	30	30	6	4	8	8
	7	18	25	8	1	19	7
	0	19	20	6	7	6	10
	6	24	300	5	1	19	6
	14	23	20	9	0	28	6
M. B.	13	20	480	5	5	10	9
M. M.	30	30	30	10	5	19	8
	19	30	25	8	0	?	8
A. N.	25	21	47	6	26	23	2
N. B.	5	28	25	9	0	19	6
	3	25	12	4	2	11	12
	5	16	15	8	2	30	4
L. J.	28	31	250	10	25	30	1
Average	14.4	23.7		6.7	5.4	18.0	

*Progesterone or anhydrohydroxy progesterone, therapy ending sixtieth day (see text).

TABLE III. SUMMARY OF OBSERVATIONS IN WHICH THERAPY WAS FOLLOWED BY AMENORRHEA

SUBJECT	BLEEDING DURING DAYS						AMENORRHEA WEEKS	RECURRENCE
	1-30	31-60	PROGESTERONE* MG.	61-70	71-100	101-130		
B. A.	16	29	30	0	6	2	12†	
A. F.	12	22	30	5	0	0	22	Yes
	10	30	25	7	0	0	19	Yes
	7	30	260	8	0	0	21	Yes
	0	26	200	6	0	0	17	Yes
	0	19	240	7	0	0	17+	
A. R.	13	30	35	9	0	0	9	Yes
	19	19	75	7	1	0	8	No
J. V.	16	17	20	5	10	0	10†	Yes
K. F.	16	21	60	7	9	9	36+†	
J. C.	8	9	40	6	0	0	36+	
L. J.	25	26	600	8	0	3	8	Yes
M. V.	30	28	30	5	0	0	9	Yes
N. B.	0	28	30	6	5	10	13†	
Average	12.3	23.8		6.1	2.2	1.7		

*Progesterone or anhydrohydroxy progesterone, therapy ending sixtieth day (see text).

†2 or 3 periods before amenorrhea began.

Observations in which the amount of progesterone given was less than 8.0 mg. (S. B.) or in which progesterone was given when the patient was not bleeding (A. O.; K. F.; J. C.) are not tabulated. Three observations with anhydrohydroxy progesterone are not tabulated. The doses used in one subject (P. K.), 120 mg. and 150 mg., are small and in both instances they were followed by larger doses so that the course immediately following was complicated by added therapy. The other untabulated observation (L. J.) was with 360 mg., but this was followed soon by 600 mg.

The general impression gained from this study is that in about one-third of the instances the menstrual periods remained essentially normal for many months after a single course of progesterone or anhydrohydroxy progesterone, whereas in another third of the instances there was a recurrence of abnormal bleeding in less than four months. In the remaining third the bleeding ceased but amenorrhea ensued. However, even in those cases in which there was a recurrence of bleeding within thirty to sixty days there seems to have been a significant reduction in the amount of bleeding taking place in the first thirty days of the follow-up period (days 71 to 100).

The average duration of bleeding in the first period (days 1 to 30) was essentially constant for all three groups of cases, about thirteen days, and similarly the average duration for the second period (days 31 to 60) was the same, about twenty-three days. These averages serve as adequate evidence that abnormal bleeding had been present for a considerable time before treatment was begun. The amount of bleeding which occurred during the third period (days 61 to 70) was about the same for all groups, about six days. From this time on, however, the reactions of the various groups are somewhat different. There was little difference in the fourth period (days 71 to 100) between those instances when normal cycles followed for at least four months (Table I) and those instances in which recurrence was to take place within four months (Table II), the average duration in this period being 5.6 and 5.1 days, respectively. There was no indication during the first month after therapy of what the future behavior was to be. In the instances in which amenorrhea followed therapy, the bleeding was considerably less, since many times the amenorrhea immediately followed the period of withdrawal bleeding. In the last period (days 101 to 130), there is an even more noticeable difference between the groups. In those instances in which normal cycles persisted (Table I), the average duration of bleeding was only 6.6 days, whereas in those instances in which recurrence had taken place (Table II) the average duration of bleeding was 17.1 days. This was almost as much as in the thirty-day period prior to and including treatment.

There is one other point which should be noted. In virtually every instance bleeding ceased (including withdrawal bleeding) within ten days of the discontinuation of therapy. The subsequent course varied

to be sure but in all instances but one (A. M.) the pattern of bleeding was measurably and significantly altered.

The effect of progesterone on the endometrium itself has not been studied in this group of cases. Many of the subjects were adolescent girls, and it was thought inadvisable to subject them to the discomfort of biopsy of the endometrium. Diagnostic curettage was done in only a few cases, but in all of those in which it was done, the endometrium showed varying degrees of hyperplasia.

DISCUSSION

The mechanism whereby progesterone alters the pattern of bleeding is not entirely clear. There is no difficulty, of course, in explaining the bleeding which occurs following the administration of the hormone, for it is well established that progesterone-deprivation is ordinarily followed by breakdown of the endometrium and bleeding (see Corner, 1939). This is the usual explanation for the course of events in the ovulatory cycle. Furthermore, the endometrium does not necessarily have to be in the late premenstrual phase for progesterone deprivation to produce bleeding. The administration of progesterone for only three or four days in the first half of the cycle may result in bleeding, even though the duration of injections is not long enough for the endometrium to show progestational changes. Even in patients with secondary amenorrhea, bleeding can be induced by the injection of progesterone for only a few days (Zondek and Rozin, 1938). In the observations reported here, there was an increase in bleeding in many instances, beginning about forty-eight hours after cessation of therapy. These patients responded in an essentially normal manner, therefore, to progesterone-deprivation. This breakdown of the endometrium is undoubtedly just as effective as a curettage in so far as interruption of bleeding is concerned. In every instance but one, there was complete interruption of bleeding for a time at least.

The course of events, after the initial deprivation bleeding had occurred, is more intriguing. In those instances where normal cycles occurred for many months, it is obvious that the disturbance in ovarian activity, which is assumed to be responsible for the abnormal bleeding, was fundamentally changed. The change from abnormal bleeding to normal cycles was so abrupt that it seems unlikely that it was due to pure chance. It seems probable, also, that this change was brought about by a change in the activity of the pituitary. Estrogens are known to affect the pituitary, although there is a difference of opinion concerning the effect; some experiments indicate inhibition and other experiments indicate stimulation.

If it be assumed that estrogen inhibits the pituitary, the following explanation would appear logical. The ovary is stimulated to a certain point, but inadequately for ovulation to occur. This results in the

continuous production of estrogen which in turn may inhibit the pituitary so that the amount of gonadotropic hormone being elaborated is never quite adequate to induce ovulation. This results either in amenorrhea or prolonged bleeding, conditions present in this type of patient. When progesterone is given, the estrogen is inhibited and consequently the pituitary is released from inhibition by the estrogen so that it may produce a quantity of gonadotropic hormone adequate to induce ovulation, in which event a normal ovulatory cycle ensues.

Another explanation can be developed from the fact that follicular growth is relatively suppressed by the presence of functional corpora lutea. Mammals which ovulate spontaneously do not ovulate when functional corpora are present nor do those animals which require the stimulus of mating (such as the rabbit) ovulate following mating when functional corpora are present. In fact, the administration of progesterone to the rabbit prevents ovulation following mating, apparently because the pituitary is unable to release gonadotropic hormone under these conditions (Makepeace, Weinstein and Friedman, 1938; Friedman, 1941). One might suppose, therefore, that progesterone itself, in the cases under discussion, had suppressed the production of gonadotropic hormone sufficiently so that the ovary was not being stimulated. This should result in widespread follicular atresia and hence in a reduction in the amount of estrogen being produced. Then, as the pituitary escaped from its inhibition by progesterone, it might produce gonadotropic hormone at a more rapid rate and hence stimulate the ovary sufficiently so that ovulation could take place.

The explanation of the observation that recurrence may take place within two or three months, or that amenorrhea may ensue is not so involved. If one assumes that progesterone in these cases had had no effect on the fundamental ovarian dysfunction, the result is precisely what would be expected. Progesterone-deprivation probably leads to a fairly complete breakdown of the endometrium, and consequently the hyperplastic endometrium was eradicated, the result being the equivalent of a curettage. The subsequent behavior would, of course, be essentially the same as before therapy except that it ordinarily requires several weeks before the endometrium becomes sufficiently hyperplastic to result in excessive bleeding.

The amount of progesterone used and the duration of therapy are such that the procedure is quite simple. It is only necessary to give about 5 mg. daily for six days. It is probably important, however, to give the hormone every day, not every second or third day. Progesterone is apparently rapidly absorbed and metabolized since deprivation bleeding ordinarily begins within forty-eight hours. The omission of a single injection may, therefore, result in a significant reduction in the amount of hormone being made available. The amount of anhydrohydroxy progesterone necessary to produce an effect similar

to 25 to 50 mg. of progesterone is not evident from this study. However, deprivation bleeding occurred when 80 mg. or more were given daily for five or six days.

It is of interest that there were many recurrences of abnormal bleeding in this group of cases. It seems probable, therefore, that prolonged bleeding, once it has been observed in a given subject, is highly indicative of the presence of a fundamental defect in the pituitary-gonadal relationship. Whether or not this disturbance is irreparable can only be determined by prolonged observation and therapy by the trial and error method. Thyroid may be very helpful in a small proportion of the cases. In two cases of the present series there was marked improvement when thyroid was given. Whether or not these subjects will mature into normal women capable of childbearing remains to be seen. One cannot refrain, however, from supposing that the disturbance in ovarian function present in these individuals is very similar to the disturbance in ovarian function observed in a certain strain of rats (Wolfe, Burack and Wright, 1940) that have a fundamental defect in their ovulating mechanism. These rats have periods of persistent estrus, due to persistence of follicles and failure of ovulation, interspersed with periods of anestrus in which there is more cornification of the vagina than usual. In addition the fertility is low. But more important, this disturbance in the pituitary-gonadal relationship is apparently hereditary. Similarly, there is a strain of mice which has a hereditary defect, resulting in a pituitary which has no eosinophiles. These mice are deficient in growth hormone and consequently remain dwarfed unless given anterior pituitary implants as extracts (Smith and MacDowell, 1930). If the inability of these individuals to ovulate regularly is a hereditary or congenital characteristic it would perhaps be unwise to attempt to induce ovulation, even were it possible to do so, since if followed by pregnancy it would tend to increase the number of individuals with the defect.

Ovarian deficiency may, of course, be produced surgically. In this study, there were four subjects in whom functional uterine bleeding developed soon after the removal of one ovary. This is not surprising since removal of one ovary and part of the remaining ovary in some rodents (rats, rabbits, and guinea pigs) disrupts the pituitary-gonadal relationship so much that ovulation fails to occur and a state of continuous estrus occurs. In the unilaterally castrated individuals reported here, progesterone seems to have been beneficial since in each case normal cycles followed the therapy for several months.

SUMMARY

The detailed menstrual records of 24 adolescent girls and young women with functional uterine bleeding are given. These subjects were given progesterone or anhydrohydroxy progesterone, and the effect on the menstrual pattern was observed over a period of many

months in most cases. In general, the administration of approximately 30 mg. of progesterone was followed by cessation of bleeding within ten days of the last injection. Progesterone deprivation bleeding occurred frequently, thereby explaining the bleeding occurring in the first few days after therapy. In about one-third of the observations, normal cycles occurred for four months or more after therapy, whereas in another third there was a recurrence in less than four months. Even in these, however, there was no recurrence in the first month. In the final third of the observations, amenorrhea followed immediately or after two or three cycles.

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DISCUSSION

DR. EMIL NOVAK, Baltimore, Md.—I do not believe that anyone is altogether satisfied with the results of organotherapy for functional bleeding. There are various reasons for this, among them is the fact that many seem to look upon functional bleeding as a single entity, and to fit all cases into one clinical and therapeutic mold. As a matter of fact, it is quite certain that the endocrine imbalance differs very much in different cases, both qualitatively and quantitatively, and our present methods do not always equip us for intelligent appraisal of each case on its individual merits.

Either the ovulatory or the anovulatory type of cycle may undergo aberrations which express themselves clinically as functional bleeding. The anovulatory, which may perhaps be considered the more primitive type, is more prone to upsets than the ovulatory, and it is this broad variety of dysfunction which is concerned in the so-called metropathia hemorrhagica of Schröder, and which is represented by the cases reported today by Dr. Allen.

One obvious comment on this paper must be that the patients reported are all very young, at least 13 of the 24 being between twelve and seventeen, inclusive. There is no doubt that in many young girls functional bleeding corrects itself, through the spontaneous establishment of ovulation, without any treatment. It would probably be possible to collect a series of the same size, with as many cures, without any organotherapy. Nor are the results better than many have reported with other hormonal methods, such as androgenic therapy.

This is not a criticism of the employment of progesterone, which is certainly as rational as any other plan, and which I also employ frequently. But there is still much to learn as to the role of progesterone in the cycle. It has physiologic properties not always easy to reconcile. Its deprivation brings about the menstrual bleeding of the ovulatory cycle; its injection in the first half of the intermenstruum brings about bleeding from an endometrium which is not progestational;

it has been shown by Hartman and Speert that in the castrated monkey, contrary to the former view, it can bring about a progestational endometrium without preliminary priming with estrogen; it undoubtedly plays a part in estrogen partition as Smith and Smith have shown; and so on.

Dr. Allen has endeavored to bring about progestational changes in the endometrium, and this is certainly possible, as many investigators have shown. But it is not certain that full progestational effects are always necessary to bring about correction of abnormal bleeding. Indeed, good results have been reported by many with much smaller dosage, although it must be admitted that many of these reports are uncritical. The physiologic effects of hormone injections do not necessarily parallel the histologic.

Finally, even though progestational effects are produced, it does not necessarily follow that the pituitary function can be beaten into a cyclic submission by regular repetitions of this highly expensive treatment. The mere existence of functional bleeding of this type presupposes a disordered and perhaps unresponsive pituitary.

Instead of injecting various hormones and attacking the problem peripherally, the as yet purely utopian ideal would be to nurse the ailing gland back to normal in some fashion or other. Aside from constitutional measures, it is possible that recent investigations on the relation of certain vitamin factors to the hormones may prove helpful. Allen and Figge have recently shown the apparent importance of the pantothenic acid factor in the production of the gonadotropic hormones by the pituitary, and Dr. Figge and I are now endeavoring to apply this observation clinically, although it is too early to speak of results.

DR. JEAN PAUL PRATT, DETROIT, MICH.—The problem considered by Dr. Allen is complex because functional bleeding is, as yet, unsatisfactorily explained. We know too little about the causes of the cycle in normal menstruation. Accepting the ovary-pituitary relationship, we must still determine what influences the pituitary. To what extent do the thyroid and other glands of internal secretion influence the pituitary?

The endocrine glands are functionally related to each other, to the autonomic nervous system, to the general state of health, to the level of nutrition, to the age of the patient, to the emotions and to the environment. It is essential, therefore, to approach this special problem by a consideration of the patient as a whole. This broad view does not preclude the investigation of special features, but it does help to keep the proper balance in the interpretation of accumulated data. The studies on progestin are commendable for even if they do not provide the answer to the treatment of functional bleeding, they contribute to our fundamental knowledge of this complex subject.

DR. JOE V. MEIGS, BOSTON, MASS. (By Invitation).—In our clinic in the Massachusetts General Hospital we have been using a method similar to Dr. Allen's and our results have been about like his. We feel that in the younger age group we have been able to relieve about 50 per cent of our patients. A good many of the older group were also relieved.

We have had patients who have been vitamin deficient. In one case a young girl with scurvy had eaten good food at home, but when away at school she ate ice cream, soda, candy, and cake instead of regular meals. She began to bleed abnormally and when she returned home there was direct evidence of scurvy.

DR. GEORGE VAN S. SMITH, BROOKLINE, MASS.—From our studies of estrogen metabolism in functional uterine bleeding, Mrs. Smith and I are convinced that an adequate amount of progesterone constitutes specific therapy, not only for the bleeding itself but also, in cases before the menopausal years, for the endocrine dysfunction which is responsible for this bleeding. The partition of the urinary

estrogens before and during this type of flow reflects a complete absence of luteal control. The administration of adequate progesterone not only stops the flow, but alters the partition of the urinary estrogens in the direction of what is found during the luteal phase of a normal cycle. Urinary findings at the start of the artificially induced period which follows progesterone are similar to those at the start of a normal postovulatory catamenia. It is because of this latter effect, namely the reproduction of a normal progestin-withdrawal bleeding, that we believe spontaneous ovulatory cycles are observed to occur in cases of functional flowing following adequate progesterone treatment. Our studies indicate that progestin-withdrawal flow is associated with a sudden increase in the rate of estrogen destruction which is not found at the start of simple estrogenic bleeding. We have come to the conclusion that progestin-withdrawal bleeding, with its associated sudden increase in estrogen destruction, provides a necessary synergistic stimulus, which I have already described, for the normal growth and maturation of the ovarian follicle.

My own clinical experience with 11 cases to date supplies the strongest support for these deductions from our laboratory findings. My present treatment for typical functional flowing is as follows: First, the bleeding is stopped with progesterone, which in a severe case may require 25 mg. a day for five days. Two to four days later another flow will begin. Counting the start of this progestin-withdrawal flow as day one, I begin on the twenty-first day a series of five daily injections of 10 mg. of progesterone plus 0.5 mg. of estradiol. The last injection is given on day 25 and three to five days later a period, normal in amount and duration, occurs.

One patient, whose functional flowing, beginning at puberty twelve years ago, had failed to respond to all conservative medical and surgical measures for eight years, was treated by this method. After 7 cycles of the above therapy she has had regular menstruation from secretory endometrium since October, 1941. Estrogen studies throughout the months of treatment indicated that spontaneous luteal secretion in this case did not begin until after the first two cycles of treatment, and did not reach the normal postovulatory level until after the last cycle of artificially induced menstruation. This was undoubtedly as recalcitrant a case as one would ordinarily encounter. From Dr. Allen's observations it would appear that repeated treatment is not necessary in all cases.

I have yet to discover whether or not spontaneous ovulatory cycles may be established consistently by this means in women with functional uterine bleeding under the early forties, or how long they will continue after cessation of treatment. At least I can tell patients when they are going to flow and how long it will last, so long as I employ this cyclic therapy.

DR. GEORGEANNA SEEGAR JONES, BALTIMORE, MD. (By Invitation).—From a purely experimental point of view, Dr. Allen's work is most interesting as it demonstrates what effect progesterone will have on uterine bleeding and opens many theoretical possibilities. In our work we have been more concerned with the practical therapeutic aspects and have approached the problem from a slightly different point of view. First, we have considered only those cases suitable for progesterone therapy where there has been functional uterine bleeding associated with endometrial hyperplasia. We have not considered the term functional uterine bleeding as synonymous endometrial hyperplasia, even in those cases occurring at puberty. Therefore every patient had had a dilatation and curettage before progesterone therapy was instituted in order to establish the diagnosis.

Second, in a study of such cases we have found that a simple dilatation and curettage is all that is necessary to relieve a number of these patients of their symptoms. Therefore, no patient has been treated with progesterone until it has been demonstrated that a therapeutic curettage will not control her bleeding.

Third, we have used a different technique. We have regarded progesterone as a form of substitution therapy and have usually considered it necessary to continue that therapy cyclically over a period of three or four months. That this method is efficacious is demonstrated by the fact that endometrial biopsies taken during the second and third month of treatment have shown an increase in secretory reaction over the first month, when, as a matter of fact, the hyperplastic gland pattern is usually still evident.

In the treatment in 111 cases of endometrial hyperplasia, before we used progesterone, the first three groups, comprising 63 cases, were under the age of 35 and more pertinent to the discussion at hand. Of the 63 cases, 25 responded satisfactorily to a simple dilatation and curettage. In the remaining 38 cases there was a recurrence of abnormal bleeding, and it was necessary to perform more radical procedures in 14 cases. These 38 cases really corresponded to our progesterone-treated cases.

Another series demonstrated the result of treatment with progesterone in 28 cases, all of which had failed to respond to a simple curettage. Only 2 of the series required hysterectomy, one not being treated on our service and the other being operated upon for chronic salpingitis. The remaining 26 cases responded to progesterone. Fourteen are well after a single course of progesterone. Three are still under the initial therapy, and 9 are asymptomatic at present but have had recurrences requiring additional progesterone courses. These 9 cases illustrate Dr. Allen's point, that progesterone therapy will not prevent recurrences of the disease in a certain number of cases.

Another series briefly summarizes the reasons why we feel that progesterone should be at least more adequately tried. Out of 111 cases, treated without the use of hormones, 33 per cent required radical procedures, whereas it has been possible to reduce this figure to 7 per cent with the use of progesterone. It seems that such a reduction is extremely worthwhile since the majority of patients are under 35 years of age.

DR. ALLEN (Closing).—Needless to say, I am well aware of the fact that controls have to be made. In this study detailed observations were made before and after therapy, and an attempt has been made to record as accurately as possible the duration of bleeding in the period just before therapy and in the period just after therapy. With the data arranged in this manner it is permissible to consider the period prior to therapy as a control period. If one were comparing the effects of progesterone with other methods of treatment, such as good food, thyroid and iron, the results obtained in one series with one method of treatment could be compared with the results in another series with another type of treatment. The results obtained are surely not due to chance, for in all instances except two or three, bleeding was measurably less in the month following therapy than in the previous control period.

I believe that in an adolescent girl of 13 or 14, it is a matter of opinion whether it is more radical to use progesterone or to do a diagnostic curettage. I prefer to use progesterone, since it is more rational than curettage, fully as effective, and no more expensive.

We have also observed pain following the progesterone-withdrawal. I might also say that in one patient with amenorrhea we have induced menstrual periods with progesterone. In this patient, two periods were induced by therapy after about fourteen months of amenorrhea. A normal period occurred one month later and then the patient became pregnant.

THE EXPERIENCE OF THE JOHNS HOPKINS HOSPITAL WITH CESAREAN SECTION*

An Analysis of 1,333 Operations

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(From the Department of Obstetrics, Johns Hopkins University and Hospital)

IN VIEW of the many statistical studies of cesarean section already published, some explanation would seem necessary in venturing to present yet another. The present group of cases appears worthy of record for a number of reasons. In the first place, it is one of the largest series thus far reported, comprising 1,333 operations, and therefore permits of statistical analysis with a minimum of sampling error. Second, 718 of these cesarean sections were performed because of contracted pelvis. These 718 cases of contracted pelvis necessitating abdominal delivery occurred in a total series of 7,226 cases of pelvic contraction. Quite apart from the size of this group of contracted pelves, and more important, is the fact that the late Dr. Whitridge Williams, from the earliest days of the clinic, insisted on meticulous pelvic mensuration, including a diagonal conjugate measurement, checked by a senior staff member. Almost half of the total operations here reported, or 43.7 per cent, were done under his surveillance. His conservatism in the use of cesarean section in contracted pelvis and his rigid adherence to contraindications are well known; and his successors have endeavored in general to follow the same policy. We, however, have had the advantage of a technical aid during the past decade which was unknown throughout the greater part of his time, namely x-ray pelvimetry, and, as we shall show, this adjunct has played an important role in the recent management of these cases and in the results achieved. We have here then a large series of contracted pelves, accurately measured, many by x-ray, and managed, we believe, in accordance with a fairly uniform and conservative policy. This affords unusual opportunity for studying the prognosis of labor in various degrees of pelvic contraction. Third, the series includes 894 classical cesarean sections performed by more than fifty operators over a span of forty-five years and is thus large and variegated enough to permit of certain conclusions about the possibilities and limitations of that operation.

TYPES OF OPERATION

In the early years of the service thirty-three vaginal cesarean sections were done, mostly for eclampsia. There were five maternal deaths, a

*Read, by Dr. Eastman, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

mortality rate of 15.1 per cent. We have excluded these from consideration not only because vaginal cesarean section is virtually an abandoned operation today, but also because the issues involved are different from those of abdominal delivery. We have also excluded eleven extraperitoneal cesarean sections (9 Waters and 2 Latzko) because their number is too small to merit attention. There were no maternal deaths in the extraperitoneal group. Nor have we included cases of rupture of the uterus or instances in which the infant weighed less than 1,500 Gm. in the belief, again, that the problems presented by such cases are different from those of cesarean section as the term is ordinarily used. This leaves 1,333 operations, of which 67.1 per cent were classical, 16.3 per cent low cervical, and 16.6 per cent cesarean section-hysterectomy (Table I). During the past decade the incidence of low cervical section has risen slightly to 20.0 per cent, while that of cesarean section-hysterectomy has fallen by about the same degree to 12.6 per cent.

TABLE I. TYPES OF CESAREAN SECTION

TYPE	CASES	PER CENT
Classical	894	67.1
Low cervical section	218	16.3
Cesarean section-hysterectomy	221	16.6
	1,333	100.0

INCIDENCE

The period over which the clinic has operated has been divided into four decades, counting backward from Dec. 31, 1941. The experience of the period 1896 to 1901 has been included with that of the first decade since the material of those six years, two cesarean sections, would obviously have no significance if analyzed separately. The incidence has been calculated on the basis of total hospital deliveries (ward and private) in which the infant weighed 1,500 Gm. or more. The incidence is avowedly high (Fig. 1), particularly in the last decade, but in evaluating these figures it is desirable to recall that our clinic admits no normal multiparas to the ward service, handles a clientele which is 50 per cent negro, and during the past six years has served as the referral center for all pathologic cases encountered in the State Board of Health's nineteen prenatal clinics scattered throughout the counties of Maryland. The marked increase in our incidence of cesarean section in the last decade is due chiefly to the institution of this referral service, but partly to a more liberal use of abdominal delivery in certain cases of placenta previa, fulminating pre-eclampsia, and in certain patients who have had previous cesarean sections.

INDICATIONS

As may be seen in Table II, the indications fall into six groups as follows: contracted pelvis and mechanical dystocia, 58.4 per cent; toxemias, 15.0 per cent; previous cesarean section, 11.2 per cent; hemorrhage, 6.6 per cent; intercurrent disease, 3.0 per cent; and unclassified, 5.8 per cent. In the first group, contracted pelvis naturally accounts for the great majority of the cases, constituting the primary indication in 44.5 per cent of the whole series. Uterine inertia is the second most common cause in this group, prompting 5.4 per cent of the operations. This heading includes, along with uterine inertia, cases of so-called

cervical dystocia, dystocia dystrophy syndrome, and prolonged labor with bad obstetric history. The term "disproportion" is not listed as a single cause since, in our experience, it is always secondary to some specific cause such as contracted pelvis, over-size baby, malpresentation, or some combination of such specific causes. In the series as a whole, fulminating pre-eclampsia accounts for 7.7 per cent of the operations, but in the last decade for 12.7 per cent, a sharp increase which will be discussed subsequently.

While it is customary to report incidence and indications in the manner we have done, a more accurate picture of the policy of a given clinic toward cesarean section may be had by reporting the percentage of cases in any specified complication which are treated by cesarean section. For instance, among our 7,226 cases of contracted pelvis, 718,

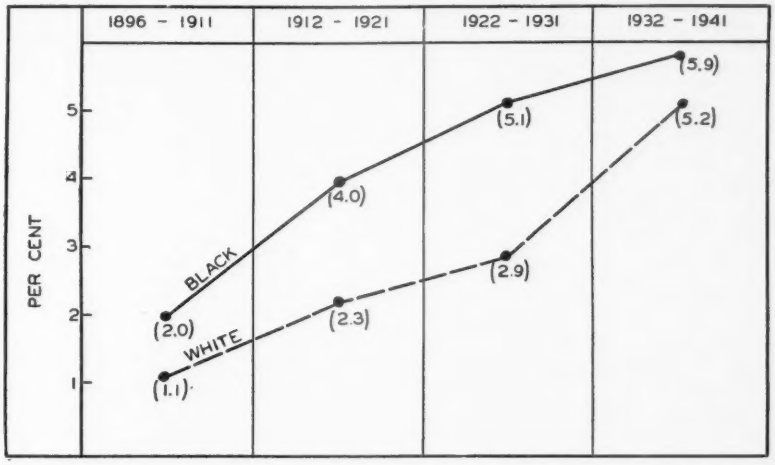


Fig. 1.—Showing the increasing incidence of cesarean section by decades and race.

TABLE II. PRIMARY INDICATIONS

		CASES	%
Contracted Pelvis and Mechanical Dystocia:	Contracted Pelvis	595	44.5
	Uterine inertia	72	5.4
	Malpresentations (45); Oversize baby (14)	59	4.4
	Tumor blocking birth canal	21	1.5
	Elderly primigravidas	35	2.6
58.4%	Total for group	781	58.4
Toxemias:	Pre-eclampsia	104	7.7
	Hypertensive vascular disease	93	6.9
	Eclampsia (before 1920)	6	0.4
15.0%	Total for group	203	15.0
Previous Cesarean Section	Previous cesarean section	115	11.2
11.2%	Total for group	115	
Hemorrhage:	Placenta previa	40	3.0
	Premature separation of placenta	48	3.6
6.6%	Total for group	88	6.6
Intercurrent Disease:	Heart disease, tuberculosis, etc.	40	3.0
3.0%	Total for group	40	
Unclassified:	Sterilization (before 1930), 34; Other 72	106	5.8
5.8%	Total for group	106	

or 9.9 per cent, were handled by abdominal delivery. During the first three decades, the incidence rose progressively to 13.8 per cent, but has fallen to 10.4 per cent in the last ten years (Fig. 2). Fig. 3 shows our incidence of cesarean section in cases of contracted pelvis according to decade and diagonal conjugate measurement. For example, among patients with diagonal conjugates between 9.0 and 9.4, only 60 per cent

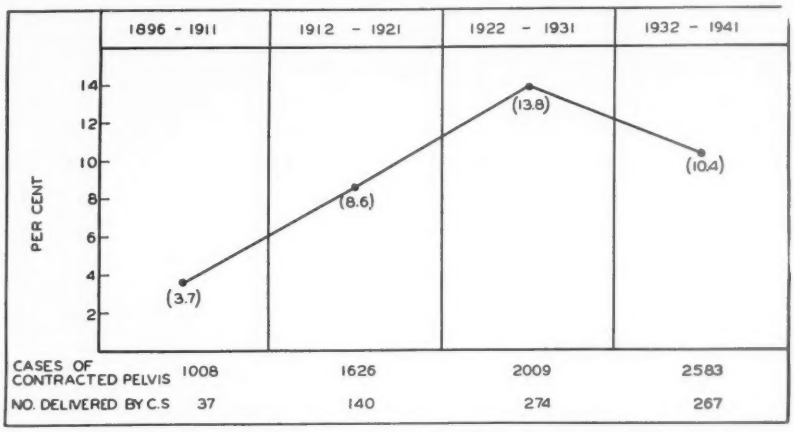


Fig. 2.—Showing incidence of cesarean section in cases of contracted pelvis (c.d. of 11.5 cm. or less) by decades. Total cases of contracted pelvis, 7,226; number delivered by cesarean section, 718; percentage delivered by cesarean section, 9.9.

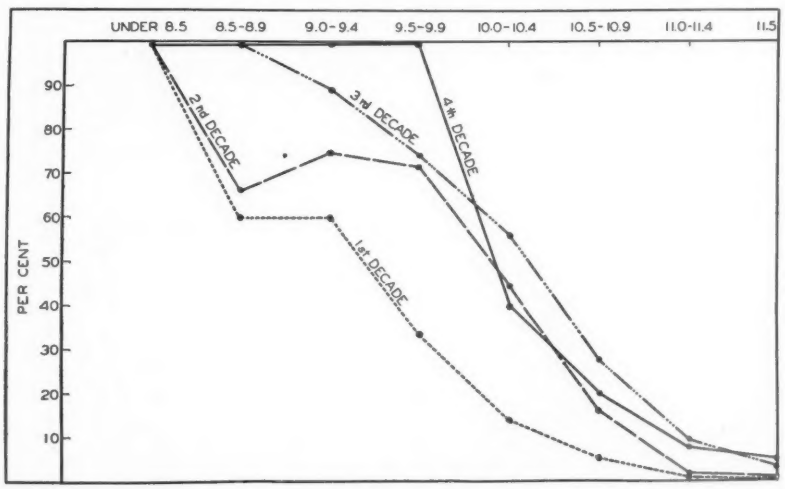
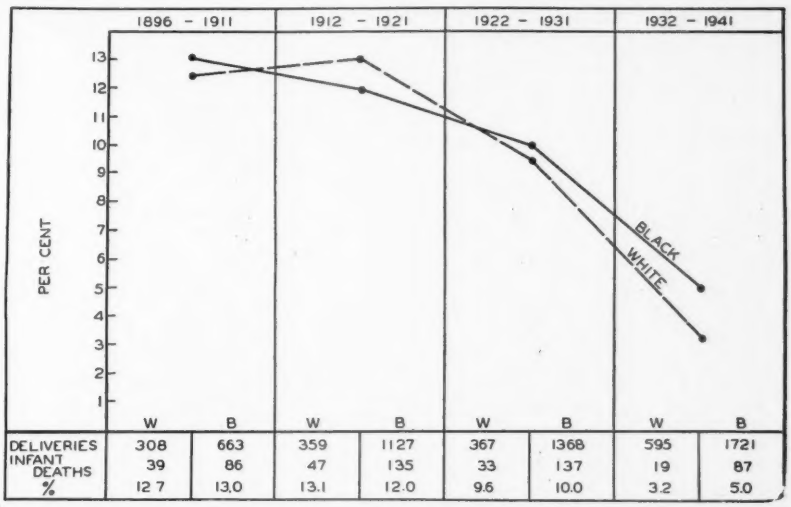


Fig. 3.—Showing incidence of cesarean section in cases of contracted pelvis according to decade and diagonal conjugate measurement.

were delivered abdominally in the first decade, 75 per cent in the second, 87.5 per cent in the third, but in the fourth ten-year period, 100 per cent. Indeed, during the past decade all women with diagonal conjugates under 10.0 have been delivered abdominally. On the other hand, in the group between 10.0 and 10.9, a substantial reduction in the incidence of cesarean section has occurred during the past decade, the percentage of abdominal deliveries being definitely less than in the last decade and in the case of the 10.0 to 10.4 group, being even lower

than in the second decade. It is this diminished incidence of cesarean section in the 10.0 to 10.9 group which has brought about the lowering in the total incidence of cesarean section in contracted pelvis as shown in Fig. 2.

Fig. 4 shows that despite the diminished incidence of cesarean section in contracted pelvis during the past decade, a dramatic reduction has occurred in our stillbirth and neonatal mortality among this group. All mortality figures reported are uncorrected. In the white, the figure has fallen to one-third that of the previous decade and in the black to one-half. We believe that there are three main factors responsible for these results. (1) X-ray pelvimetry has made possible a more precise



	W	B	W	B	W	B	W	B
DELIVERIES	308	663	359	1127	367	1368	595	1721
INFANT DEATHS	39	86	47	135	33	137	19	87
%	12 7	13.0	13.1	12.0	9.6	10.0	3.2	5.0

Fig. 4.—Showing the stillbirth and neonatal mortality rate by decade in cases of contracted pelvis delivered vaginally (6,508 deliveries).

estimation of pelvic size and architecture in the troublesome group with diagonal conjugates between 10.0 and 11.0 and has permitted a more correct prognosis in regard to the possibilities of pelvic delivery. Diagonal conjugate measurements above 11.5 almost always rule out contractions of the inlet, but measurements between 10.0 and 11.0 may reflect imperfectly the true or obstetric conjugate diameter. Thus, among women with diagonal conjugates of 10.5 cm., the obstetric conjugate may vary between 8.2 and 10.3, a range of more than two centimeters. X-ray study of the architecture of the midpelvis also affords valuable information as to which cases may be delivered vaginally and which demand cesarean section. In our experience, then, this technical adjunct has played an important role not only in reducing infant mortality in the contracted pelvis group but in eliminating unnecessary cesarean section among these patients. (2) Another factor which may be credited with the results shown in Fig. 3 is the realization that tests of labor in patients with contracted pelvis, when carried beyond thirty hours, yield a fetal mortality rate in excess of 30 per cent, as shown some years ago in our clinic by Peckham and Kuder. With rare exceptions a careful weighing of all the factors concerned, including x-ray findings, after twelve hours of labor, is adequate to yield a proper decision as to whether or not abdominal delivery is necessary. (3) A

third factor which has proved helpful in our hands in establishing the prognosis of labor in contracted pelves is the behavior of the cervix. Stated briefly, in degrees of contracted pelvis incompatible with delivery from below, the cervix rarely dilates satisfactorily. By way of supporting this statement we have studied forty-nine labors in women with contracted pelves in which cesarean section was finally performed after thirty or more hours of labor and found that the cervix had reached full dilatation in only eight of these cases, or less than one-sixth; in twenty-nine of the cases, or one-half, the dilatation was less than 5 cm.; in thirteen or one-fourth, it was less than 3 cm. even after thirty hours. To be sure, some of these cases may have been associated with uterine inertia, but the clinical fact remains that tests of labor which ultimately fail are usually stigmatized from the very beginning by a cervix which does not dilate; and conversely, among those which are ultimately successful, the cervix is usually near complete dilatation after twelve hours.

Turning now to pre-eclampsia, the percentage of cases of that complication treated by cesarean section has risen from 2.0 per cent in the first three decades to 7.8 per cent in the last ten-year period. In other words, during the recent period about one pre-eclamptic in every thirteen is delivered by the abdominal route. With occasional exceptions, all of the pre-eclamptics so delivered fulfilled the following criteria: the disease appeared fulminating with convulsions imminent and did not respond to medicinal treatment; the pregnancy was four or more weeks from the expected date of confinement and conditions were unfavorable for rupture of the membranes, that is, the head was high and the cervix long, hard and closed. We believe that cesarean section is indicated under such circumstances. The reason for this attitude is not so much the fear of convulsions as the fact that the long period of time necessary to carry such patients before vaginal delivery can be effected safely, imposes a greater risk in the way of permanent vascular damage, than is represented by the general risk of cesarean section.

Our incidence of cesarean section in other common complications is as follows: previous cesarean section (no other indication), 53.4 per cent for the series as a whole, 63.6 per cent for the past decade; placenta previa, 20.8 per cent for the series as a whole, 38.0 per cent for the past decade; premature separation of the placenta, 27.3 per cent for the series as a whole, 31.0 per cent for the past decade; elderly primigravidas, 18.6 per cent for the series as a whole, 25.0 per cent for the past decade.

TABLE III. MATERNAL MORTALITY ACCORDING TO DECADE AND TYPE

1333 Operations	38 Deaths	Total mortality	2.8%
894 Classical	20 Deaths	Classical mortality	2.2%
218 Low Cervical Section	6 Deaths	Low cervical section mortality	2.7%
221 Cesarean section-hysterectomy	11 Deaths	Cesarean section-hysterectomy mortality	5.0%

TYPE OF OPERATION	1896-1911			1912-1921			1922-1931			1932-1941		
	CASES	DEATHS	%	CASES	DEATHS	%	CASES	DEATHS	%	CASES	DEATHS	%
Classical	24	4	16.6	113	2	1.8	244	6	2.4	513	8	1.5
Low cervical section	0	0	0	0	0	0	66	3	4.5	152	3	2.0
Cesarean section-hysterectomy	17	1	5.8	43	1	2.3	76	8	10.5	85	2	2.2

MATERNAL MORTALITY

As shown is Table III, among the 1,333 operations extending back to 1896, there were 38 deaths, a gross uncorrected mortality rate of 2.8 per cent. Among the 894 classical operations, there were 20 deaths, a rate of 2.2 per cent. The respective mortality rates for low cervical section and cesarean section hysterectomy were 2.7 and 5.0 per cent. During the past decade there were 513 classical cesarean sections with 8 maternal deaths, a mortality rate of 1.5 per cent. The opinion has been expressed that any death rate above 1 per cent in cesarean section is too high; and we are in accord with this view so far as the white race is concerned, but doubt if it can be approached in the black. As shown in Fig. 5, the total maternal mortality for the white race was 2.0 per cent and for the black, 3.5 per cent. During the past decade the corresponding percentages were 0.8 and 2.8, respectively (Fig. 6.). That this difference is not due to a preponderance of neglected cases of labor in the black race is shown by Fig. 7. Here it will be seen that even in elective cases the mortality of the colored race is two and one-half times that of the white.

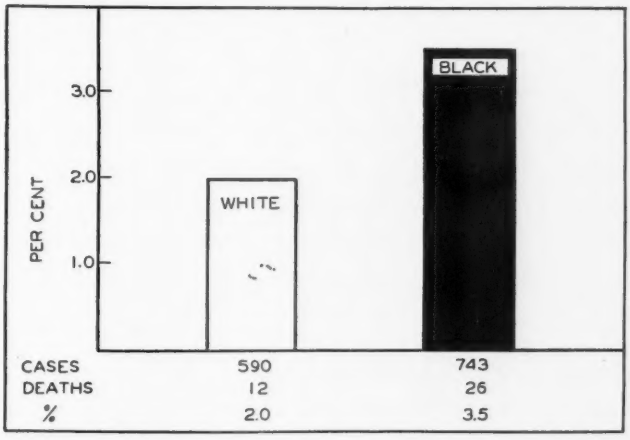


Fig. 5.—Showing the maternal mortality in the total series according to race.

Causes of Maternal Deaths.—The causes of the 38 maternal deaths are shown in Table IV. The most common cause was shock and hemorrhage. A critical analysis of these 9 cases would suggest, on hindsight, that the following errors of commission and omission played important roles in these fatalities: (1) The imposition of a shocking operation (cesarean section, hysterectomy in 5 of the 9) on patients already shocked from premature separation of the placenta, or exhausted by prolonged labor; (2) failure to protect such patients against shock by the liberal use of blood transfusions before, during, and after these operations. Less than one-fourth of the deaths (6 of the 38) were due to generalized peritonitis, but an equal number were the result of paralytic ileus alone, as attested by autopsy. In this latter group the earlier and more persistent use of continuous gastric suction might have saved some of these women. Of the 4 anesthetic deaths, 3 occurred in women who had been in labor over thirty hours, a circumstance attesting the fact that patients exhausted by long labors are poor anesthetic risks as well as poor risks from the viewpoint of shock.

During recent years a number of clinics have reported a reduction in their materal mortality rates in cesarean section and have attributed this to abandoning the classical operation in favor of the low cervical technique. From the viewpoint of straight thinking it is worth while noting that our maternal mortality with classical cesarean section in

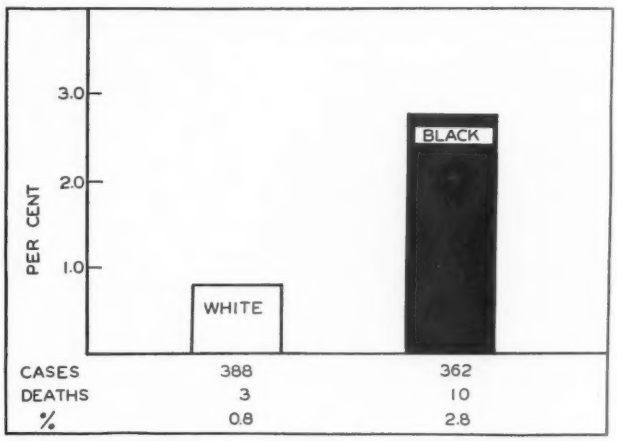


Fig. 6.—Showing the maternal mortality in the last decade according to race.

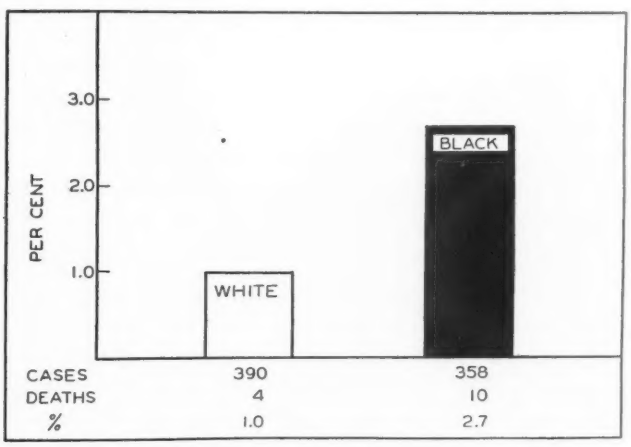


Fig. 7.—Showing the maternal mortality in elective cesarean section according to race.

white women, counting from 1896, was 1.1 per cent in 354 elective cases; in the last decade it was 0.7 per cent in 275 similar cases; no patients died from peritonitis, as attested by autopsy. We believe, accordingly, that prior to the onset of labor, classical cesarean section will give as good immediate results as low cervical provided that contraindications are rigidly observed. Hence, we suspect that the improved mortality rates which have been credited to the low cervical technique are in many instances the result of stricter observance of contraindications, better judgment in the selection of cases and more blood transfusions. So far

TABLE IV. CAUSES OF 38 MATERNAL DEATHS IN 1,333 CESAREAN SECTIONS (MORTALITY 2.8%)

Deaths Due Directly to Operation			
1. Shock and hemorrhage	9	Classical	4
		Cesarean section-hysterectomy	5
2. Generalized peritonitis	6	Classical	4
		Cesarean section-hysterectomy	1
		Low cesarean section	1
3. Ileus alone. (No general peritonitis; no mechanical obstruction)	6	Classical	3
		Cesarean section-hysterectomy	1
		Low cesarean section	2
4. Ileus due to mechanical obstruction	3	Classical	3
5. Thrombophlebitis with septicemia	4	Classical	2
		Cesarean section-hysterectomy	1
		Low cesarean section	1
6. Anesthesia (including one aspiration pneumonia with death on first post-operative day)	4		
	32		
Deaths Due to Intercurrent Disease			
Hypertensive vascular disease			2
Acute thromboendocarditis			1
Cerebral hemorrhage in pre-eclampsia			1
Primary meningitis			1
Miliary tuberculosis			1
			6

as the late results are concerned, that is, the integrity of the scar, an inquiry into the literature shows a woeful lack of statistically valid, factual information supporting the supposed superiority of the low segment scar.

The odds in the present series are weighted heavily against low cervical cesarean section inasmuch as this operation, until very recent years, has been reserved for potentially infected cases and any attempt to compare these cases statistically with our classical series would not be equitable. Nevertheless, our experience suggests that even this procedure becomes increasingly hazardous after eighteen hours of labor and in such cases had best be superseded either by cesarean section-hysterectomy or an extraperitoneal operation.

DISCUSSION

DR. FRED L. ADAIR, CHICAGO, ILL.—There are two, possibly three, major differences between the series at the Chicago Lying-In Hospital and the series at the Johns Hopkins Hospital. In the first place, our series is limited to the white race. Second, our series is based predominantly on the low cervical operation, and, third, although it was not mentioned in the paper, I believe that our percentage of cases done under local anesthesia is much higher than in Dr. Eastman's clinic.

We have reported 1,000 cesarean sections covering a period from 1931 to 1938 in 18,009 deliveries, an incidence of 5.5 per cent. From March 1, 1938, to March 1, 1942, there were 11,232 deliveries with 497 cesarean sections, an incidence of 4.4 per cent. I would like to point out that during this latter period we have insisted more vigorously on reaching a decision for or against cesarean section after twelve

hours of ruptured membranes or twenty-four hours of labor. This has not resulted in an increase of cesarean section notwithstanding this rule.

In the first series of 1,000 cases the morbidity was 43.8 per cent. In the second series the morbidity was 32.9 per cent, a decrease of nearly 11 per cent. In the first series there was a mortality of 8 cases, or 0.8 per cent; in the second series a mortality of 2 cases, or 0.4 per cent, a decrease of 50 per cent in our mortality. And I might say that 50 per cent of the mortality in the first series was associated with infection, whereas in the second series there was no mortality from infection. It is very important then to recognize the contraindications against cesarean section, especially from the standpoint of the possibility of an infection which may terminate fatally.

Another point I think is extremely important which Dr. Eastman did not mention is the question of outlet contraction. It is important to recognize it early as it is a bar frequently to natural or instrumental delivery. If it is not diagnosed early the contraindications for cesarean section have arisen before it is recognized and, of course, then the operation is too late to be advantageous.

Another point is that there is a cumulative risk from cesarean section. A woman who has an initial cesarean section is exposed to the risk of a second operation. In the morbidity series we found that 25.6 per cent of approximately 197 cases had had one previous cesarean section, and that 6.7 per cent had had more than one cesarean section.

The lower segment operation was done in 87.2 per cent of the morbidity cases; the classical operation in only 0.6 per cent. Hysterectomy was associated with cesarean section in 10.3 per cent, and the vaginal operation was done in 1.8 per cent, which corresponds rather closely with the figures given by Dr. Eastman. We did a sterilization operation in 42 per cent of the morbidity cases.

The indications for cesarean section were hemorrhage in 11.5 per cent; toxemia in 19.5 per cent; a cardiac condition in 5.5 per cent; previous cesarean section in 6.7 per cent; coexistent pathology in 4.2 per cent; disproportion and dystocia in 52.5 per cent.

Local anesthesia was used exclusively in 53 per cent; combined with general anesthesia in 20.9 per cent; and general anesthesia alone in 26 per cent. These figures apply to the morbidity series and not to the entire series of cases.

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—No discourse on cesarean section should omit a consideration of fetal mortality. At the Methodist Hospital of Brooklyn, from April 1, 1924, to Aug. 1, 1941, there were a total of 31,242 deliveries with a total of 2,089 fetal deaths or a rate of 6.6 per cent. In this series there were 1,116 cesarean sections with a total of 68 fetal deaths, giving a rate of 6 per cent. I appreciate the fact that there were considerable more vaginal deliveries than deliveries by cesarean section; however, the figures do bring out the point that fetal survival is not necessarily simply a matter of performing cesarean section.

Let us take, for the sake of comparison, the fetal mortality rate in cesarean section in 3 other representative hospitals. We find the following: The Chicago Lying-in, 6.7 per cent in 1,000 cesarean sections; The Woman's Hospital, New York, 6.69 per cent in 912 cesarean sections; The Philadelphia Lying-in, 10.8 per cent in 830 cesarean sections. Our rate of 6.0 per cent in 1,116 sections compares favorably with these figures.

In our series, prematurity constituted the largest group of nonsurvivals (25, or 4.0 per cent) and this is in line with other reports. Cesarean section apparently gives no better assurance of survival of the viable premature than well-managed vaginal delivery. Congenital anomalies made up the next largest group in our

series of nonsurvivals (12 or 1.9 per cent), and here I should like to point out that, whenever possible, every cesarean section should be preceded by an x-ray examination of the fetus in utero and thus rule out, at least, certain types of anomalies. Neonatal infection, eclampsia, hemorrhagic disease of newborn, and intracranial hemorrhage were among other causes listed.

In conclusion, I should like to emphasize again that cesarean section carries with it a sizable fetal mortality and that we should constantly reiterate this fact in all our discussions of cesarean section to the end that the lay public, as well as the medical profession, may more fully realize that abdominal section is "no positive assurance of a live baby."

DR. WILLIAM R. NICHOLSON, PHILADELPHIA, PA.—The anesthesia is an important consideration in determining the fetal mortality in cesarean section. For some time I have made a practice of having the woman brought into the operating room, placed on the table, catheterized, and the abdomen prepared before any anesthetic is given. A very slight anesthesia, not much deeper than the first stage, is given and as soon as the woman is unconscious the incision is made. The baby is probably only two minutes under very moderate anesthesia before its delivery. This has made a tremendous difference. Formerly I did not do a cesarean section unless I had a man on the other side of the table perfectly competent to take over the patient, thus enabling me to attend to the resuscitation of the baby. Under this plan of reduced amount of anesthesia for the baby in utero we find that the baby inspires as soon as delivered.

DR. EASTMAN (Closing).—Since the subject of cesarean section runs almost the whole gamut of obstetrics, it was obviously impossible to deal with more than a few aspects of the problem in this survey. With regard to Dr. Adair's comments upon outlet contraction, our experience has been that outlet contraction *alone* is rarely an indication for abdominal delivery. In a primigravida with a breech presentation and outlet contraction, or in a woman with a large baby and outlet contraction, it may occasionally be necessary, but in our series there are only 12 instances in which cesarean section was performed solely on the grounds of a diminished bi-ischial diameter.

In regard to our fetal mortality, this figure was 6.0 per cent for the entire series. The greater number of these stillbirths and neonatal deaths were the result of premature separation of the placenta, placenta previa, and toxemias of pregnancy.

THE POSSIBLE ETIOLOGIC ROLE OF GYNECOLOGIC LESIONS IN THE PRODUCTION OF HYPERTENSION*

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THAT arterial hypertension is frequently associated with renal disease has been accepted as a fact since the classic contributions of Bright. The recent brilliant experimental work of Goldblatt, Paged, and others, however, has led to a renewed interest in this subject which has resulted in the recording of much careful investigation, both experimental and clinical. The recent literature is so replete with articles, many of which contain complete bibliographies, that a comprehensive review would be not only time-consuming but superfluous.

Since the observations to be recorded herewith are at least suggestive that hypertension may result from partial ureteral occlusion, a brief review of the literature of this phase of the subject is appropriate.

From the field of animal experimentation the reports are meager and conflicting. Hinman and Morrison's[1] work with experimental hydronephrosis in rabbits led them to suspect that renal blood flow was diminished. Enger, Gerstner and Sarre[2] using direct measurements found that when the intraureteral pressure was over 60 there was a significant fall in renal blood flow, often as much as 35 per cent. Levy, Mason, Harrison and Blalock[3] measured renal blood flow after ureteral occlusion in eight dogs; the average reduction was 41 per cent. Three of their dogs developed hypertension, and Megibow, Friedberg, Rodbard and Katz[4] reported hypertension in 6 of 7 dogs after bilateral complete ureteral occlusion, and in 5 of 7 dogs after partial occlusion of both ureters. These workers have explained the frequent occurrence of hypertension in their animals on the basis of renal ischemia. Eichelberger[5] on the contrary was unable to demonstrate the development of hypertension in any of 20 dogs subjected to partial ureteral constriction, even though half of her dogs progressed into uremia.

On the clinical side Schroeder and Steele[6] have observed bilateral hydronephrosis in 11 and unilateral hydronephrosis in 20 of 71 patients with essential hypertension. Approaching the subject from the opposite angle, Braasch, Walters and Hammer[7] found hypertension in only 72, or 22 per cent, of 372 patients with hydronephrosis; but in 10, or 34.4 per cent, of 29 patients in whom the hydronephrotic kidney was removed, or the hydronephrosis corrected by conservative surgical measures, the blood pressure returned to normal and remained so for from one to five years following operation. Such observations can only lead to the conclusion that hydronephrosis due to ureteral obstruction

*Read at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

must in some individuals at least result in arterial hypertension. The failure of every individual so to respond to the presence of hydronephrosis merely falls in line with similar observations regarding many types of renal disease. Even the severest forms of atrophic pyelonephritis with marked sclerosis of the arterioles and small arteries of the kidney, the type of lesion most commonly considered as playing a large etiologic role in the production of hypertension, may at times occur in individuals with perfectly normal blood pressures. This fact has been well demonstrated recently by Crabtree and Chaset[8] as well as others. To explain the lack of uniformity of response in arterial tension to similar renal lesions on the part of different individuals is difficult and beyond the scope of this paper.

The observations to be recorded herein were begun more or less accidentally. About three years ago one of us (Everett), with the collaboration of W. J. Sturgis,[9] decided to study the effect of a variety of major gynecologic disorders upon the urinary tracts. In undertaking this study we hoped to be able to observe personally findings recorded previously in the case of large pelvic tumors such as uterine fibroids and ovarian cysts by Kretschmer and Kanter,[10] and in the case of uterine prolapse by Brettauer and Rubin[11] and by Wallingford.[12] In addition, we wished to make similar observations on patients suffering from pelvic inflammatory disease, a phase of the subject concerning which practically nothing could be found in the literature. Exactly 50 per cent of

TABLE I. URINARY TRACT DISORDERS OBSERVED BEFORE THE INSTITUTION OF TREATMENT IN 100 PATIENTS WITH VARIOUS GYNECOLOGIC LESIONS:
A—UPPER TRACT DILATATION

TYPE OF LESION	NO. STUDIED	BILATERAL DILATATION		UNILATERAL DILATATION	
		NO.	%	NO.	%
1. Uterine fibroids					
a. Above pelvic brim with salpingitis	13	8	61.5	2	15.4
b. Above pelvic brim without salpingitis	17	6	35.3	4	23.5
c. Below pelvic brim with salpingitis	8	1	12.5	1	12.5
d. Below pelvic brim without salpingitis	9	1	11.1	2	22.2
2. Chronic salpingitis	9	1	11.1	3	33.3
3. Subacute salpingitis with pelvic masses	12	4	33.3	3	25.0
4. Pelvic abscess	7	2	28.6	2	28.6
5. Ovarian cyst	4+1*	1+1*	40.0		
6. Carcinoma of ovary	5	3	60.0		
7. Complete procidentia of uterus	3+1*	1	25.0	1	25.0
8. Incomplete prolapse of uterus with cystocele	10	3	30.0	1	10.0
9. Cystocele without prolapse of uterus	3	0	0	0	0
Total	100	31	31.0	19	19.0

*Cases also included in one of the groups with uterine fibroids.

our subjects showed some degree of either bilateral or unilateral pelvic and ureteral dilatation. The distribution of such dilatation among various gynecologic diagnostic groups is shown in Table I, and the results of observation of urinary tract abnormalities other than dilatation is shown in Table II. From Table II it can also be seen that 36 per cent of the 100 patients were found to have some degree of arterial hypertension. This seemed an extraordinarily high incidence of this condition for a group of patients whose average age was only 37.06 years, and of whom only 14 were more than fifty years of age. Further analysis revealed that 25 of the patients with hypertension were in the group of 50 showing pelvic and ureteral dilatation, an incidence of 50 per cent for this group, while only 11 or 22 per cent, of those without upper urinary tract dilatation were hypertensive.

TABLE II. OBSERVATION ON THE URINARY TRACTS OTHER THAN THE PRESENCE OR ABSENCE OF UPPER TRACT DILATATION IN 100 GYNECOLOGIC PATIENTS

TYPE OF CONDITION	NO. STUDIED	BLADDER INFECTION		UPPER TRACT INFECTION		DIMINISHED FUNCTION		HYPERTENSION	
		NO.	%	NO.	%	NO.	%	NO.	%
Uterine fibroids without pelvic inflammation	26	8	30.8	4	15.4	3	11.5	12	46.1
Uterine fibroids with pelvic inflammation	21	6	28.6	1	4.8	3	14.3	9	42.8
Pelvic inflammation without fibroids	28	5	18.0	1	3.6	3	10.7	5	18.0
Other conditions	25	6	24.0	1	4.0	1	4.0	10	40.0
Total	100	23	23.0	7	7.0	10	10.0	36	36

Of the 23 bladder infections 11 were in the group without upper tract dilatation and 12 in that with dilatation.

Of the 7 upper tract infections only 1 was in the group without dilatation.

None of the 10 cases with diminished function were in the group without dilatation.

Of the 36 hypertensive patients 11 were among the 50 patients without dilatation, an incidence of 22 per cent for the group, and 25 were in the group with dilatation, or an incidence of 50 per cent for this group.

Average age of the 100 patients: 37.06 years. Only 14 were more than 50 years of age.

Following these observations it was decided to continue the studies upon as many of these 100 patients as possible in order to observe the effects of appropriate gynecologic treatment upon the dilated urinary tracts and upon the hypertension. For the purpose of these studies the 100 patients were divided into 4 groups as follows:

Group I, 39 patients with neither urinary tract dilatation nor hypertension.

Group II, 25 patients with both urinary tract dilatation and hypertension.

Group III, 25 patients with urinary tract dilatation without hypertension.

Group IV, 11 patients with hypertension without urinary tract dilatation.

TABLE III. OBSERVATION ON THE UPPER URINARY TRACTS FOLLOWING APPROPRIATE GYNECOLOGIC TREATMENT IN 30 OF THE 50 PATIENTS SHOWING UPPER TRACT DILATATION BEFORE TREATMENT

TYPE OF CONDITION	NO. FOLLOWED	RETURNED TO NORMAL		PARTIAL REGRESSION		NO CHANGE	
		NO.	%	NO.	%	NO.	%
Uterine fibroids without pelvic inflammation	8	5	62.5	1	12.5	2	25.0
Uterine fibroids with pelvic inflammation	8	4	50.0	2	25.0	2	25.0
Pelvic inflammatory disease, chronic, subacute and pelvic abscess	10	3	30.0	5	50.0	2	20.0
Ovarian cyst	1			1	100.0		
Uterine prolapse with cystocele	3	1	33.3			2	66.6
Total	30	13	43.3	9	30.0	8	26.7
All cases with pelvic inflammation	18	7	38.9	7	38.9	4	22.2
Uncomplicated tumors (myomas and ovarian cysts)	9	5	55.5	2	22.2	2	22.2

Of the 13 patients whose upper tracts returned to normal none had shown upper tract infection and only 3 had shown bladder infection in the original studies.

Of the 17 patients whose upper tracts failed to return to normal 3 had shown upper tract infections and 6 bladder infections in the original studies.

TABLE IV. FOLLOW-UP STUDIES ON HYPERTENSION

	GROUP I: 39 CASES NO DILATATION NO HYPERTENSION	GROUP II: 25 CASES DILATATION AND HYPERTENSION	GROUP III: 25 CASES DILATATION WITHOUT HYPERTENSION	GROUP IV: 11 CASES HYPERTENSION WITHOUT DILATATION
Definite hypertension. Systolic blood pressure above 160 and/or diastolic blood pressure above 95	0	14	0	5
Borderline hypertension. Systolic blood pressure 140-160 and/or diastolic blood pressure 90-95	0	11	0	6
Number followed	20	13 6 definite 7 borderline	14	2 definite 2 borderline
Improved		1 definite to normal 1 definite to borderline 4 borderline to normal 2 definite temporarily or moderately improved		
No change	19	1 definite 2 borderline	11	4
Blood pressure increased	1 developed definite hypertension	1 borderline to definite 1 definite and higher	2 normal to definite 1 normal to borderline	

Fig. 1.

Fig. 2.

Fig. 1.—Left retrograde pyelogram of a colored patient, aged 37 years, with uterine fibroids extending above the umbilicus. Intravenous pyelograms had shown similar dilatation of the right pelvis and ureter, but this plate was made because of poor visualization of the left tract by the excretory method. The patient's blood pressure at this time was 226/132.

Fig. 2.—Bilateral retrograde pyelogram of the same patient illustrated in Fig. 1, six weeks after supravaginal hysteromyomectomy and left salpingo-oophorectomy. It can be noted that the urinary tracts have returned to essentially normal proportions. The patient's blood pressure had been reduced to 154/84 at the time of discharge from the hospital and was 195/110 when this plate was made. In the course of a year, however, it returned to its preoperative level.

Fig. 3.

Fig. 4.

Fig. 3.—Preoperative intravenous pyelograms of a colored woman, aged 43, with large uterine fibroids, chronic salpingitis and left ovarian abscess.

Fig. 4.—Preoperative retrograde pyelogram of the same patient as Fig. 3, made to obtain better visualization of the left urinary tract. The preoperative blood pressure was 144/80. Operation was supravaginal hysteromyomectomy, and bilateral salpingo-oophorectomy.

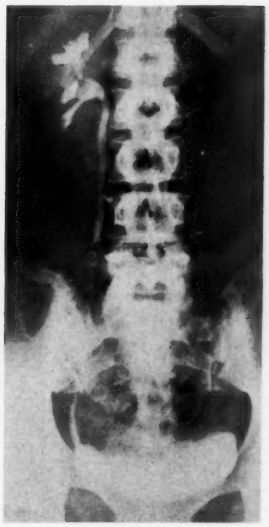

Fig. 5.

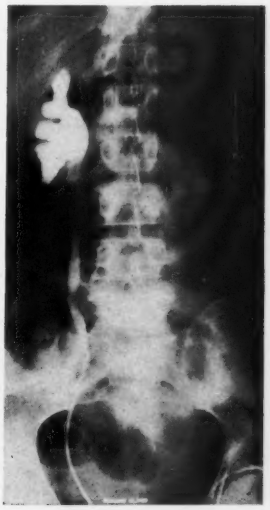

Fig. 6.

Fig. 5.—Retrograde right pyelogram of the same patient as illustrated in Figs. 3 and 4. Note the return to normal of the pelvis and ureter. On the left side, the one upon which the ovarian abscess had been situated, dilatation of the pelvis and ureter equal to that present preoperatively persisted. After 19 months the patient's blood pressure had increased to 150/100.

Fig. 6.—Right retrograde pyelogram of a colored woman, aged 53 years, with pelvic cellulitis and bilateral *E. coli* infection of the upper urinary tracts. There was marked diminution of the phenolsulphonephthalein output from both kidneys. She was treated with sulfanilamide and diathermy with resulting eradication of the urinary tract infection, return of the phenolsulphonephthalein output to normal, and marked improvement in the pelvic cellulitis. The blood pressure before treatment was normal 128/78.

Fig. 7.—Posttreatment right pyelogram of the same patient as Fig. 6. There is some decrease in the size of the pelvis and ureter but definite dilatation is still present. On the left side, which was similar to the right before treatment, there was no decrease in size. After twenty months the patient's blood pressure had risen to 160/110.

Hypertension was classified as either definite or borderline, those patients with a systolic blood pressure of more than 160 and/or a diastolic pressure of more than 95 being assigned to the definite group. In the borderline group were included those patients with a systolic pressure of 140 to 160 and/or a diastolic pressure of 90 to 95.

The results of treatment upon the urinary tracts in 30 of the 50 patients who had shown pelvic and ureteral dilatation are shown in Table III. In Table IV are shown the results of blood pressure studies

Fig. 8.

Fig. 9.

Figs. 8 and 9.—Right and left pyelograms of a white patient, aged 64 years, with complete procidentia of eight years' duration. The preoperative blood pressure was 200/100. There was no change in the pyelograms following correction of the prolapse by the Richardson composite operation, but there was slight improvement in the hypertension, the blood pressure being 162/92 at the time of discharge from the hospital and 175/100 after nineteen months.

made from one to two years following completion of treatment. Table V is an attempt to correlate the follow-up studies on hypertension with those on the urinary tracts for the group, while Tables VI and VII show the details of some individual patients in this regard.

In addition to the 100 patients originally studied, a second hundred with pelvic masses at least sufficiently large to fill the cul-de-sac of Douglas, but who were not subjected to urologic examination, have been analyzed for the incidence of hypertension. This condition was found in 44 of this group, the average age of which was 39.4 years. In the total 200 patients studied, therefore, an incidence of 40 per cent of arterial hypertension was found. In Table VIII the incidence of hypertension according to race and age is analyzed and compared with a control group of 200 patients, 100 white and 100 colored, taken from

routine admissions to the gynecologic wards. Such a group of necessity includes a considerable number of patients with major gynecologic disorders, such as are being considered herein, but it also includes a sufficient number of patients without pelvic masses or uterine prolapse to make it worth while for the sake of comparison.

TABLE V. URINARY TRACT STUDIES IN PATIENTS FOLLOWED FOR HYPERTENSION

	ORIGINAL STUDY		FOLLOW-UP STUDY		
	INFECTED UPPER TRACTS	DIMINISHED FUNCTION	NO.	NORMAL	PERSISTENT DILATATION
Group II: 8 cases improved	0	3	7	5	2
Group II: 5 cases with blood pressure unchanged or increased	3	2	3	1	2
Group III: 3 cases which developed hypertension	2	2	3	1	2
Group III: 11 cases in which blood pressure remained normal	0	0	8	4	4

In Table IX the incidence of hypertension in the two groups is shown in comparison with that found by Wetherby[13] in a group of 3,250 women. Wetherby has defined hypertension in this group to include all patients with a systolic blood pressure of 150 or more. He has made no division as to race, so for the purpose of comparison with his figures this division is omitted in our groups also. However, in analyzing our results it must be borne in mind that a large proportion, 77.5 per cent, of our patients were colored. In a study of 1,198 colored and 989 white hypertensive patients admitted to the Louisville City Hospital during the same period, Weiss and Prusmack[14] found that hypertension occurred a decade earlier in the negroes than in the whites.

DISCUSSION

Tables VIII and IX show conclusively that the incidence of hypertension in the group of patients under consideration is definitely higher than in two control groups of similar age. This difference is most striking in those patients from 30 to 39 years of age, and the incidence of the gynecologic disorders under consideration is also highest among patients falling into this age group. These findings taken alone are suggestive that these gynecologic disorders may play some etiologic role in the production of hypertension. The studies of the urinary tracts in the first 100 patients showed that the incidence of hypertension was more than twice as great in those patients who showed evidence of urinary tract stasis as in those in whom such stasis was absent. This finding is at least suggestive that if these gynecologic conditions do play an etiologic role in the production of hypertension, they probably do so as a result of their interference with the normal function of the urinary tracts.

TABLE VI. DETAILS OF 14 CASES FOLLOWED FOR HYPERTENSION IN GROUP II: UPPER TRACT DILATATION AND HYPERTENSION

	SERIES NO.	AGE	RACE	ORIGINAL DIAGNOSIS	TREATMENT	AMOUNT OF DILATATION	UPPER TRACT INFECTION	DIMINISHED FUNCTION	BLOOD PRESSURE: ADMISSION	BLOOD PRESSURE: DISCHARGE	BLOOD PRESSURE: FOLLOW-UP	FOLLOW-UP OF URINARY TRACTS
Definite hypertension returned to normal. 1 case	32	34	c	Adenomyoma Salpingitis chronic	Hysterectomy Right salpingo-oophorectomy	Right +	0	0	144/102		120/80 18 mo.	Not done
4 cases with borderline hypertension returned to normal.	4	45	c	Fibroids Salpingitis chronic	Hysterectomy Right salpingo-oophorectomy Left salpingectomy	Bilateral +++	0	0	132/95	122/85	110/78 21 mo.	Normal
	19	44	c	Adenomyoma Tuboovarian inflammatory cysts	Hysterectomy Bilateral salpingo-oophorectomy	Bilateral ++	0	0	135/90		110/80 14 mo.	Normal
	75	21	c	Pelvic abscess	Laparotomy with drainage twice Hysterectomy Bilateral salpingo-oophorectomy	Right +++	0	Right	140/90	130/80	118/70 16 mo.	Normal
	85	20	c	Pelvic abscess	Posterior colpotomy	Bilateral +++	0	0	140/80		124/84 15 mo.	Right, normal Left, no change

Improved from definite to borderline group	41	55	w	Prolapse, second degree	Manchester operation	Bilateral +	0	0	194/104		160/94	16 mo.	Normal
3 cases with definite hypertension improved. 1 became borderline. 2 remained definite	18	40	c	Fibroids. Tubo-ovarian inflammatory cysts	Hysterectomy Bilateral salpingo-oophorectomy	Bilateral +	0	0	170/110	134/90	130/70 154/104	4 mo. 19 mo.	No change
	5	37	c	Fibroids	Hysterectomy Left salpingo-oophorectomy	Bilateral +++	0	Bilateral	226/132	154/84	195/110 225/115	6 wk. 8 mo.	Pyelograms normal. Function still diminished
	8	64	w	Complete procidentia	Richardson's composite operation for prolapse	Bilateral +++	0	Right	200/100	162/92	175/100	19 mo.	No change in x-rays. Function normal. Cultures positive
3 cases, 2 borderline and 1 definite. No change	16	48	w	Fibroids, bilateral hydrosalpinx. Carcinoma of cervix, Stage I	Panhysterectomy Bilateral salpingo-oophorectomy	Left +	0	0	145/78		160/68	19 mo.	No change
	23	39	c	Fibroids Bilateral pyosalpinx	Hysterectomy Bilateral salpingectomy	Bilateral +	0	0	155/85		144/94	16 mo.	Normal
	40	68	w	Complete procidentia	Pessary. No operation	Right ++	Right	0	188/120	180/112	198/120	18 mo.	Not done
2 cases with increased hypertension	6	43	c	Fibroids Ovarian abscess	Hysterectomy Bilateral salpingo-oophorectomy	Bilateral +++	+	Bilateral	144/80		152/100	19 mo.	Right, normal. Persistent infection. Left, no change
	38	35	c	Fibroids	Hysterectomy	Right ++	+	+	190/110	160/100	210/140	17 mo.	Not done

TABLE VII. DETAILS OF 14 CASES FOLLOWED FOR HYPERTENSION IN GROUP III; DILATATION WITHOUT HYPERTENSION

	SERIES NO.	AGE	RACE	ORIGINAL DIAGNOSIS	TREATMENT	AMOUNT OF DILATATION	UPPER TRACT INFECTION	DIMINISHED FUNCTION	BLOOD PRESSURE			FOLLOW-UP OF URINARY TRACTS
									ORIGINAL	FOLLOW-UP		
3 developed hypertension 2 definite 1 borderline	17	53	c	Subacute salpingitis. Pelvic cellulitis	Diathermy. Sulfanilamide	Bilateral +++	Bilateral	Bilateral	128/78	160/110	20 mo.	No change left. Partial regression right. Function normal
	71	41	w	Adenomyoma	Panhysterectomy	Right +	0	Right	134/80	152/92	16 mo.	No change
	74	34	c	Fibroids. Right ovarian cyst. Right broad ligament cyst	Hysterectomy. Right salpingo-oophorectomy	Right +++ Left +	Right	0	130/85	154/100	15 mo.	Normal
11 patients whose blood pressure remained normal	22	32	c	Fibroids	Hysterectomy. Left salpingo-oophorectomy	Bilateral +	0	0	120/85	108/70	19 mo.	Normal
	44	34	c	Subacute salpingitis	Hysterectomy. Left salpingo-oophorectomy. Right salpingectomy	Right +	0	0	120/75	118/75	13 mo.	Normal
	69	27	w	Ovarian cyst, right	Right salpingo-oophorectomy	Bilateral +++	0	0	100/70	104/58	16 mo.	Nearly normal

68	38	c	Subacute salpingitis. Tuboovarian abscess, left	Sulfanilamide. Diathermy	Left +	0	0	132/78	110/70	18 mo.	Nearly normal
67	33	c	Pelvic cyst, inflammatory	Posterior colpotomy	Right +++	0	0	118/82	124/68	18 mo.	Moderate decrease
31	27	c	Fibroids. Chronic salpingitis	Hysterectomy. Bilateral salpingo-oophorectomy	Bilateral ++	0	0	110/80	118/86	18 mo.	Moderate decrease, right. No change, left
78	21	c	Chronic salpingitis. Cystic ovary, left	Hysterectomy. Left salpingo-oophorectomy. Right salpingectomy	Right +	0	0	130/80	120/70	15 mo.	No change
99	37	w	Retroversion. First-degree descensus	Richardson's composite operation for prolapse	Right ++	0	0	118/72	118/86	15 mo.	No change
46	37	c	Bilateral tuboovarian abscess	Abdominal drainage, right abscess	Bilateral ++	0	0	138/82	120/80	16 mo.	Not done
65	38	c	Chronic bilateral salpingitis	Diathermy	Right +	0	0	135/80	122/72	21 mo.	Not done
81	44	c	Fibroids	Hysterectomy. Left salpingo-oophorectomy	Right +	0	0	120/78	118/70	16 mo.	Not done

TABLE VIII. COMPARISON OF THE INCIDENCE OF HYPERTENSION ACCORDING TO AGE AND RACE IN THE 200 PATIENTS STUDIED AND 200 CONTROLS

AGE	WHITE						COLORED					
	NO. OF CASES		NO. HYPERTENSIVE		PER CENT HYPERTENSIVE		NO. OF CASES		NO. HYPERTENSIVE		PER CENT HYPERTENSIVE	
	STUDY	CONTROL	STUDY	CONTROL	STUDY	CONTROL	STUDY	CONTROL	STUDY	CONTROL	STUDY	CONTROL
Under 20	0	0	–	–	–	–	2	0	1	–	50	–
20-29	6	6	0	0	0	0	26	13	4	3	15.2	23
30-39	14	33	2	2	14.3	6.06	68	41	25	10	36.8	24.4
40-49	15	27	5	8	33.3	29.6	49	31	27	7	55.1	22.6
50-59	7	18	6	9	85.7	50.0	9	10	6	7	66.7	70.0
60-69	3	10	3	5	100.0	50.0	1	4	1	3	100.0	75.0
70-79	0	6	–	2	–	33.3	0	1	–	1	–	100.0
Total	45	100	16	26	35.5	26.0	155	100	64	31	41.3	31.0

TABLE IX. COMPARISON OF PERCENTAGE INCIDENCE OF HYPERTENSION BY AGE DECADES IN 200 PATIENTS STUDIED, AUTHOR'S CONTROLS, AND 3,250 WOMEN REPORTED BY WETHERBY

AGE	SERIES STUDIED	AUTHOR'S CONTROL	3,250 WOMEN WETHERBY
Under 20	50.0		1.05
20-29	12.5	15.8	3.01
30-39	32.9	17.6	10.33
40-49	50.0	25.9	40.89
50-59	75.0	57.1	50.50
60-69	100.0	57.0	66.82
70-79			

We feel that such a concept may offer a possible explanation for the syndrome sometimes referred to as "myoma heart," which has hitherto not been adequately explained. We furthermore feel that in planning gynecologic treatment for patients suffering from such diseases as tend to interfere with the normal function of the urinary tract, therapeutic methods should be chosen which tend as nearly as possible to remove completely such interference. This we believe is particularly pertinent regarding the selection of operation or irradiation therapy for uterine fibroids. The latter type of therapy, although it may relieve the obvious symptoms of fibroids such as uterine bleeding, does not remove the tumors. Furthermore, as has been shown previously in two publications by one of us (Everett[15, 16]), this type of therapy per se sometimes results in fibrosis with stricture formation in the lower ureters. We, therefore, feel that before selecting irradiation therapy for uterine fibroids, the presence of hydronephrosis and hydroureter should be eliminated by intravenous urography, and indeed that probably the best policy is to confine such therapy to that relatively small group of patients in whom there is some absolute contraindication to surgical intervention. Furthermore, it is not unusual to encounter patients near the menopausal age with uterine fibroids which are producing no symptoms. It has been our tendency in the past to defer operation with the assurance that if the condition remains asymptomatic until the menopause is fully established no further trouble is likely to ensue. We now feel that before such a policy is decided upon, the absence of ureteral compression by the fibroid masses should be determined by means of intravenous urography.

In Table III an attempt was made to find some common factor such as the presence of urinary tract infection or of pelvic inflammation which might explain the failure of the urinary tracts to return to normal following appropriate gynecologic treatment. Neither of these factors seemed to answer this question adequately, and although it is difficult to show statistically or in tabulated form, it has been our impression from studying the patients individually that a very important factor in this regard is the length of time over which the gynecologic lesions in question have persisted. It is conceivable that a segment of

ureter, subjected to pressure over a long period of time by a pelvic mass or a prolapsed uterine vessel, might undergo fibrotic changes resulting in stricture formation sufficient to prevent its return to normal after removal of the original cause of compression. Then too, in some instances intrinsic strictures may have developed independently of the gynecologic lesions. In the group of patients studied, however, the symptoms of ureteral stricture so often detailed and stressed by Hunner have been conspicuously absent. We therefore feel that in the case of pelvic inflammatory disease and the lesser degrees of uterine prolapse especially, surgical intervention should not be too long delayed. If in patients with pelvic inflammation, masses persist after a sufficient conservative regime of palliation and chemotherapy to produce abatement of signs and symptoms of acute inflammation, these masses should be removed. In young women with relaxation of the pelvic floor and moderate uterine prolapse, repair operations of conservative types, compatible with future childbearing, should be carried out in preference to delaying operation until the patients' families are complete in order to do more radical procedures.

CONCLUSIONS

We believe that the foregoing study warrants the following conclusions:

1. That arterial hypertension occurs with greater frequency in patients suffering from various types of large pelvic masses and from uterine prolapse than it does generally in women of similar age.

2. That the hypertension in such a group probably results frequently from interference with normal ureteral drainage caused by the gynecologic lesion in question.

3. That the therapy selected for the treatment of such gynecologic lesions should be of a type that tends to relieve as completely as possible such interference with ureteral drainage; namely, surgical removal of the pelvic masses and adequate repair of uterine prolapse.

4. That such therapy should not be delayed too long merely because of the absence of marked symptoms on the part of the patient.

The diodrast used for intravenous urography in these studies was furnished by the Winthrop Chemical Company.

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DISCUSSION

DR. ROBERT A. KIMBROUGH, PHILADELPHIA, PA.—In view of an increasing amount of evidence there can be little doubt that the various obstructive uropathies not infrequently cause arterial hypertension. This fact is attested not only by the occurrence of hypertension in this group of cases but by the improvement or actual relief of hypertension after the obstructive lesions have been eliminated.

The series of cases presented by Dr. Everett, while not extensive, is sufficiently large and so carefully studied that it constitutes an important contribution to this chain of evidence. One wonders, however, whether more detailed investigation might not have revealed other more likely causes for hypertension in some of his patients.

The high incidence of both hypertension and ureteral obstruction in this rather ordinary run of gynecologic cases constitutes a potent reason for early removal of pelvic masses and not too long delayed correction of prolapsus.

I am sure that many of us have chosen irradiation therapy for hypertensive patients with large myomas rather than subject them to the risks of surgical removal. In view of this study we possibly have been withholding from such patients the best chance of relieving their hypertension. It would seem quite reasonable in these cases, as Dr. Everett has suggested, that surgical removal of large myomas is indicated either as prophylaxis against or treatment of the accompanying urinary stasis and hypertension.

DR. EVERETT (closing).—I had no intention of indicating that hypertension had been relieved to any great extent, although this seems to have happened in a few patients. The number of cases in which this occurred, however, was too small to make that deduction of much value. To predict the relief of hypertension in individual cases would be very difficult.

The causes of hypertension of renal origin are so involved with the anatomy and physiology of the kidney that those who have done the most work on the subject, particularly Page, believe that hypertension is largely due to inadequate or impaired blood supply of the kidney. According to the work of Goldblatt, this usually results from some compression of the arterial blood supply.

There are several methods, rather complicated ones, of determining the diminution of the blood supply. Howard Taylor has recently reported a series of patients with obstetric toxemias, in which he studied the comparison of the inulin and diodrast clearance tests. Diminution of tubular function, as indicated by a decreased diodrast clearance, is supposed to show a diminution of blood supply to the tubular epithelium which results in the secretion into the system of pressor substances. These tests are usually done on the total renal substance representing both kidneys. In cases where the surgical relief of hypertension is proposed, a better idea of the prognosis may be obtained by differential inulin and diodrast clearance tests performed on the individual kidneys. I have carried out such procedures in a few cases, but they are almost too tedious and time-consuming to apply to a large series.

GONORRHEA IN THE FEMALE AND ITS TREATMENT WITH SULFONAMIDES*

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SOME of the earliest medical writings make mention, in both man and woman, of the disease we now know as gonorrhea. It remained, however, for Neisser (1879) to identify and Bumm (1885) to culture the specific microorganism. Vonderlehr and Usilton[1] of the United States Public Health Service stated in 1937 that at least one million persons in this country acquire gonorrhea each year, of whom approximately one-fourth (230,000) are women. During the past four years there has been approximately three to four thousand female cases reported in New York City each year. It is felt by responsible officials that this record is far from complete.

A knowledge of the natural course of this disease is essential in the interpretation of therapeutic measures. It is probable that in many cases the disease remains localized to the lower genitourinary tract and does not invade beyond the depth of the mucous membrane surfaces. Furthermore, in the majority of these patients the infection gradually and spontaneously dies out in these sites. The urethra is usually cured first and the time necessary for spontaneous cure probably varies from a few weeks to even years in some cases. Invasion of the upper genital tract most frequently follows menstruation, the termination of a pregnancy, or the application of physical and chemical agents employed in treatment. It is quite uncommon for the infection to persist for any long period of time in the Fallopian tubes or peritoneal cavity. Our experience in this respect is, in general, in agreement with that of Curtis,[2] which was reported twenty years ago. In our opinion the use of local antiseptics and other older methods of treatment rarely affected favorably the clinical course and, at times, they initiated extension of the disease that later caused irreparable damage. The acceptance of these facts means that we are not dealing with a fatal disease and accordingly any therapy must be absolutely safe.

Specific fever therapy, based on the thermal death time of the infecting strain of gonococcus, was introduced by Carpenter and his associates[3] in 1932 and constituted the first really specific therapy employed in the treatment of this disease. Carpenter and others[4] have reported over

*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

80 per cent of cures where this principle was adhered to following a single treatment. The method, however, is now employed only to a very limited extent and chiefly in the treatment of sulfonamide failures. Clinical reports on the use of sulfanilamide started appearing during the summer of 1937 and have since completely revolutionized our therapeutic armamentarium. Our investigations with this compound were commenced shortly thereafter. Sulfathiazole in late 1939 and sulfadiazine in 1940 were introduced for clinical investigation and were at once employed in the studies to be reported. While there have been many favorable clinical reports on the use of the former drug in gonorrhea very few on the use of the latter compound have as yet appeared in the literature. The advent of these newer methods of treatment has aroused much interest and the imagination of many public health officials has been stirred to the point where they now believe it possible to eliminate this most prevalent of all infectious diseases. With these facts in mind it would appear to be an appropriate time to review some phases of our work on this problem.

It is our purpose to detail our experiences from two main points of view. The first has reference to diagnosis and an attempt will be made to correlate subjective symptoms and signs with more exact laboratory studies. Data will be presented, demonstrating the superiority of cultural methods as compared to the study of smears. The second problem deals largely with therapy and is confined entirely to the evaluation of three drugs, i.e., sulfanilamide, sulfathiazole, and sulfadiazine. Variations in dosage, duration of treatment, the effect of various social and economic factors, pregnancy, race, age, and other differences will be considered briefly. Toxicity and dangers associated with the administration of the various drugs will be commented upon.

The study is based upon observations made on 185 admissions to the New York Lying-in Hospital of 158 patients all of whom had gonorrhea. Twenty-five patients were admitted a second time and two on a third occasion. Patients not admitted or where there was any question as to the diagnosis are excluded from the present study. Sixty-four patients were treated with sulfanilamide, 62 with sulfathiazole, and 59 with sulfadiazine. In the charts that follow the three groups are designated according to the sulfonamide employed irrespective of whether the data have reference to therapy or not. Dosage, toxic symptoms, fluid balance, blood and urine studies, and social behavior were all known factors, many of which are undeterminable in the case of ambulatory patients. A comparison of factors, such as age, color, site of disease, etc., is necessary because at the time the study was started only sulfanilamide, of the drugs employed, was available. The other compounds were used as they were introduced for investigational purposes, and accordingly it was not possible to alternate patients at the time of admission with respect to the drug employed.

A study of such factors as age, color, marital status, and the incidence of pregnancy prior to, during, and following treatment revealed no important differences in the three groups. Fig. 1 illustrates the distribution of patients with respect to the nature of the infection. The number thought to have acute initial infections was practically the same in each group. There was a somewhat larger number of chronic infections in the sulfanilamide group. Most instances of recurrence of the disease were treated with sulfathiazole or sulfadiazine for reasons that will later become evident. Fig. 2 demonstrates the close similarity in the three groups as far as the site of disease is concerned. Nearly 60 per cent of the entire group were thought to have the disease confined entirely to the lower genitourinary tract. It was impossible to demonstrate the presence of the disease in the genital tract in one of two patients who had suppurative arthritis despite repeated positive cultures from the joint exudate.

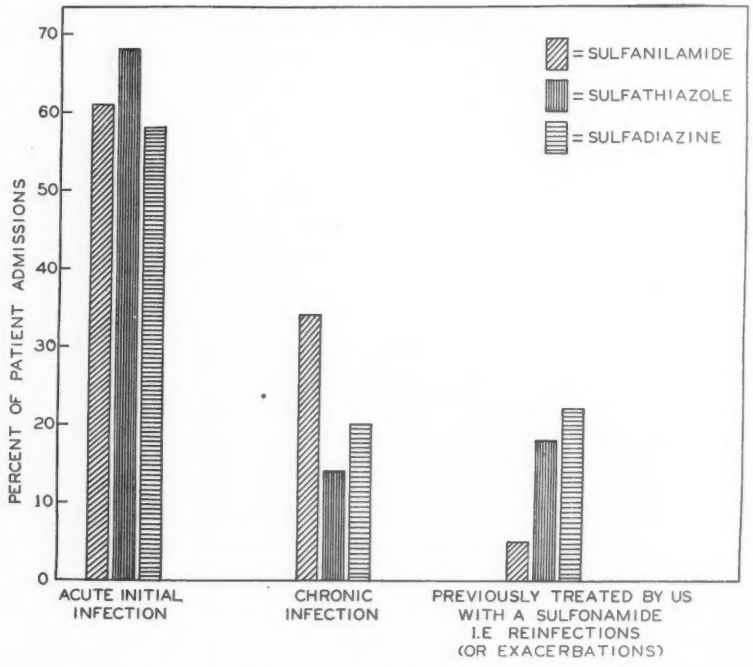

Fig. 1.—Nature of infection.

Serologic or other positive evidence of syphilis was present at the time of admission on 19 occasions (10.3 per cent), four instances in each of the sulfanilamide and sulfadiazine groups and 11 times in the sulfanilamide group. A few patients were admitted with early infectious syphilis and for the most part were treated for that disease until they were rendered noninfectious before instituting the sulfonamide therapy.

DIAGNOSIS

The diagnosis of gonorrhea has long been a difficult, and in some respects, a controversial problem. It is true that a clinical history

correlated with the physical findings may be very suggestive. The complement fixation test has largely fallen into disrepute in this country. Torrey,[5] on the other hand, still feels that it is a highly specific diagnostic aid, if the antigen is of high sensitivity, low in anticomplimentary property and all proper precautions in conducting the test are exercised. Assuming this to be true many negative tests during the early stages and many positive reactions after the cure of the disease would almost certainly be obtained. These points become especially significant at the present time in the control of treatment when the disease may actually be cured in a matter of hours. Thus from a laboratory point of view we are confined largely to the use of smears and cultures.

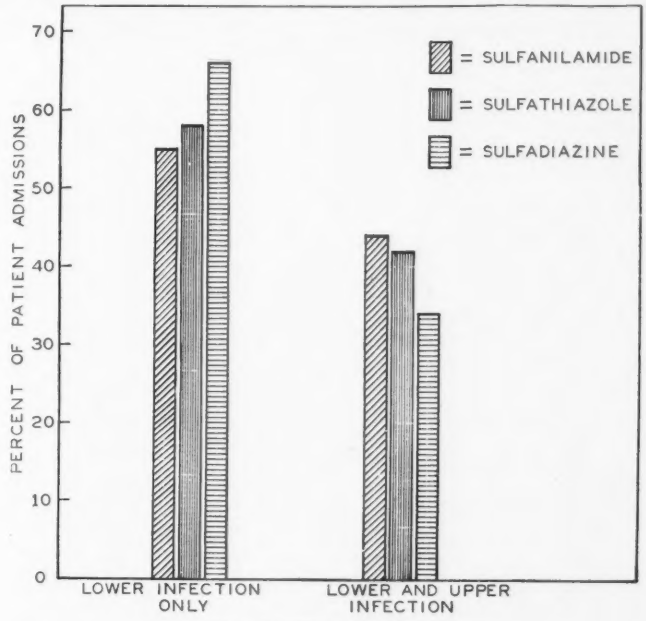

Fig. 2.—Site of disease.

ROUTINE EMPLOYED

With adequate exposure of the vulva and a good source of light, the labia are held far apart, bringing the external urethral meatus into view. The area just within the meatus is first cleaned with a sterile applicator which is then discarded. The urethra is massaged from back forward and from either side to the midline. The exudate so expressed is collected on a small, moist sterile swab. Smears are prepared by the "rolling technique" on clean glass slides, and after reapplying the swab to the urethra it is plated directly on a chocolate agar plate (Difco*). Cervical exudate for similar studies is obtained from the endocervix after cleaning the vaginal vault with a sterile cotton ball. In the event that bacteriologic quantitative determinations are desired, the technique is the same, excepting the swab is rotated three complete turns in either the urethra or cervix. The swab is then inoculated and

*Difco Laboratories, Incorporated, Detroit, Michigan.

emulsified in 0.5 c.c. of Douglas broth and 0.2 c.c. of the suspension is then inoculated on the surface of the plates.

The laboratory procedure used is essentially the modification by Leahy and Carpenter,[6] of the technique proposed by McLeod and his co-authors.[7]

All smears were stained by Gram's method. With respect to the interpretation of smears a "positive" implies the organisms to be intracellular and otherwise characteristic. The chocolate agar plates were placed in an inverted position in airtight jars, replacing approximately 12 per cent of the air with 10 per cent carbon dioxide.

Observations of cultures were made at the end of a forty-eight hour incubation period at 37° C.; smears were made of the typical colonies and stained by Gram's method. Frequently in the case of initial cultures the colonies were subcultured to carbohydrate media for the fermentation reaction to ascertain final confirmation.

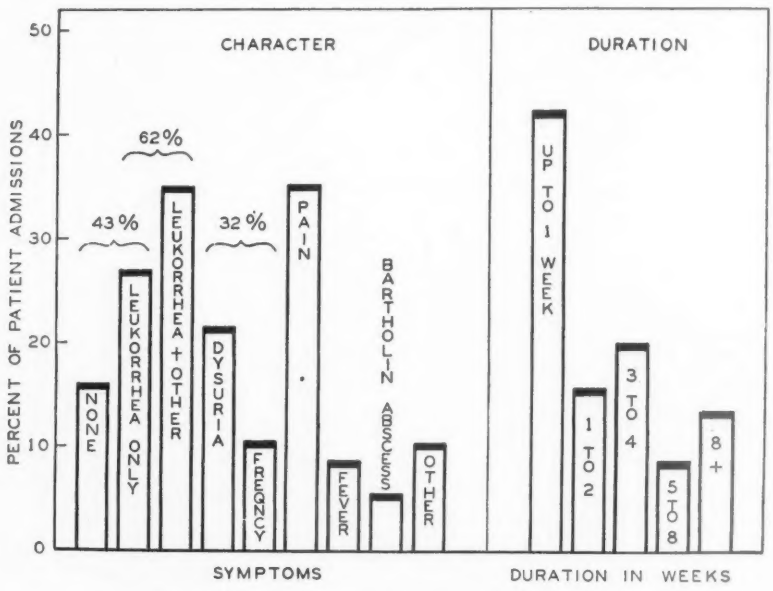

Fig. 3.—Symptoms on admission (entire series).

All subsequent cultures were examined by the oxydase reaction described by McLeod, et al.[7] The reagent is applied by pipetting 1 to 2 c.c. of a 1 per cent aqueous solution of p-aminodimethyl aniline monohydrochloride.* The plate is observed for evidence of color changes in the colonies. The color reactions occurring in sequence are pink, maroon, and finally black with intermediary changes. Smears are then made and stained by Gram's method.

Since the dye is toxic for the gonococcus, if subcultures are desired, it is necessary to transfer the suspected colony in the pink stage. The oxidation progressing to the black stage of the colony will render the cells nonviable, therefore, preventing growth in subculture. However, the dye does not interfere with Gram's stain.

*Eastman Kodak Company, Rochester, New York.

Fig. 3 illustrates the frequency of the occurrence of the more common symptoms. It is significant to note that 16 per cent had no complaints and an additional 27 per cent gave leucorrhea as their only symptom, a total of 43 per cent. Urinary tract symptoms were present in one-third and abdominal pain was complained of in approximately an equal number of cases. The patients without symptoms were discovered, for the most part, through epidemiologic studies carried out by the Department of Health of New York City, and referred to us for treatment. The duration of symptoms played no role as far as we could determine in the therapeutic results.

In Fig. 4 the diagnostic results of smear and culture studies are displayed. The first section of the chart is based on an analysis of the results of the first specimen *only* obtained from each patient. The similarity of results in each of the groups is striking. If the data are

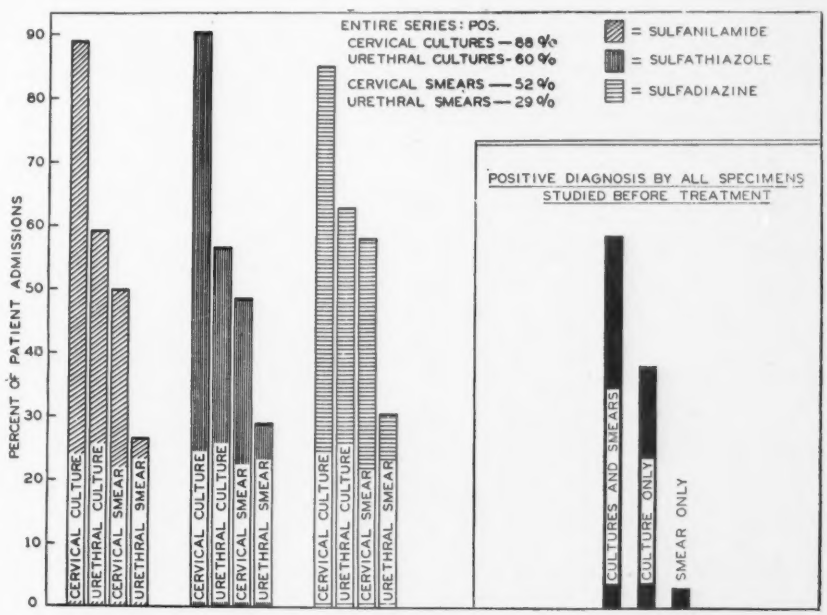

Fig. 4.—Positive diagnosis by first specimen studied before treatment.

combined and approximations employed we may say that nine-tenths of the cervical cultures and only one-half of the cervical smears were positive. Sixty per cent of the urethral cultures and one-half that number of urethral smears were found to be positive.

If we study the results of *all* cultures and smears taken before the onset of treatment we may say that a positive laboratory diagnosis was based on both positive cultures and smears in nearly 60 per cent, on positive cultures *only* in over 35 per cent and positive smears alone in a relatively insignificant number of cases. In addition, a number of the smears revealed extracellular forms and might be designated "suspicious" but are rightfully excluded from the positive group. Even if

these were included they would raise the positive cervical smears but 12 per cent and the urethral smears 9 per cent.

Fig. 5 illustrates the results of all cultures and smears employed in the diagnosis, control of treatment, and in follow-up studies. These data are based on a total of 8,765 laboratory procedures. Many negative specimens are introduced by this means of analysis so that the number of positive results appears relatively small. However, the essential differences, as far as the relative value of the four procedures with relation to positives, are maintained. Therefore, it becomes evident that if cultures are omitted from any diagnostic routine, approximately 35 per cent of patients who actually have the disease will be undiagnosed.

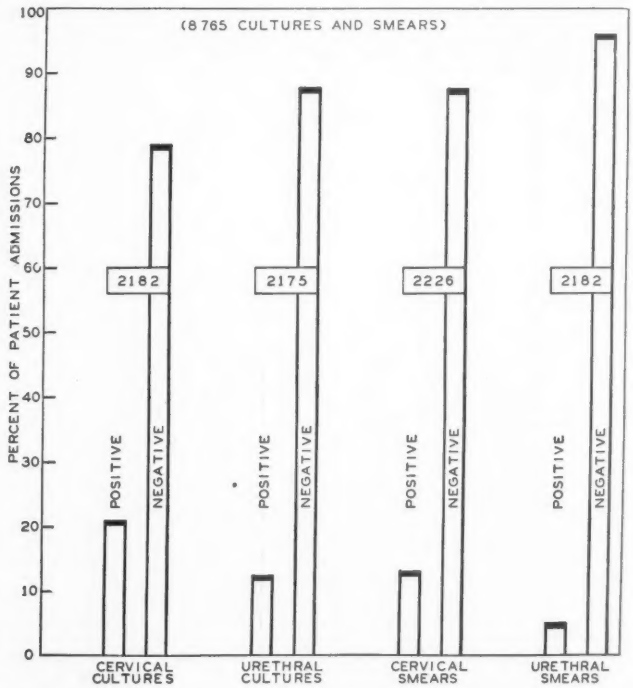

Fig. 5.—Results of all cultures and smears employed in diagnosis control of treatment and follow-up.

If suspicious cases are included as positive, this percentage would be reduced to approximately 25 per cent. Many of the cases recognized by cultural methods only are likely to be chronic "carriers" who, for the most part, may be asymtomatic, and it is this group which constitutes a serious public health problem. In general it may be said that either smears or cultures will usually give positive results in the acute exudative stage of the process but for the accurate diagnosis of the latent phase of the disease cultural methods should be employed.

TREATMENT

The duration of hospitalization was frequently considerably longer than actually necessary in order to repeat diagnostic procedures and

to make many other observations that seemed desirable for this study. In general, however, it may be seen from Fig. 6 that the sulfanilamide group was hospitalized appreciably longer than the other two groups. In fact, two-thirds of the sulfathiazole and sulfadiazine groups were discharged by the tenth day at which time only one-fourth of the sulfanilamide group were permitted to leave. We feel that hospitalization for therapy is highly desirable but not absolutely essential.

In over 80 per cent of instances treatment was started within nine days from the time the diagnosis was made. Delay was chiefly due to locating patients, repetition of diagnostic procedures and the treatment of infectious syphilis prior to the institution of sulfonamide therapy. In our experience, we found no correlation between the specificity of the therapy and the duration of symptoms or the interval from diagnosis to treatment.

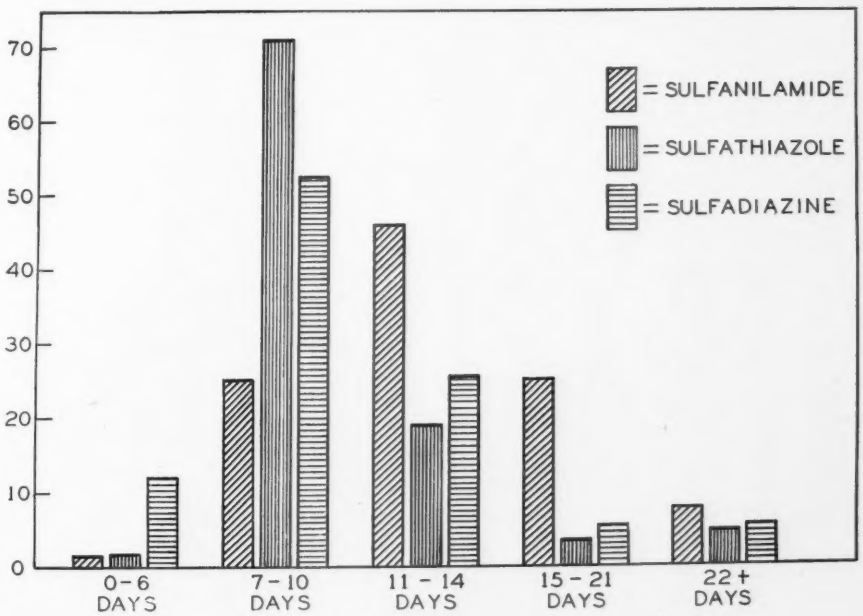

Fig. 6.—Days of hospitalization.

Fig. 7 illustrates various differences in the daily and total dosage employed, the duration of treatment in days and correlates the incidence of recurrence of the disease and the failures with each of these factors. It is seen that wide variations in therapeutic methods were utilized. The daily dosage varied from 2 to 7 Gm., the total dosage from 7 to 73 Gm., and the number of days of treatment from 1 to 13. The instances of prolonged and high dosage were in patients with unusual circumstances or for experimental reasons, and were few in number. The most commonly employed daily dose was 5.4 Gm. with sulfanilamide, 6.0 Gm. with sulfathiazole and 4 Gm. with sulfadiazine. The most frequently used total dosage was between 36 and 40 Gm. for sulfanilamide and sulfathiazole, and 20 and 29 Gm. for sulfadiazine. The treat-

ment was continued somewhat longer in the sulfanilamide group than in the other groups. During the progress of the study we gradually employed both a smaller daily and total dosage and in addition, the duration of treatment tended to be of shorter duration. A careful survey of this chart shows that the majority of the patients that subsequently developed a recurrence of the disease, were treated with a relatively large dosage over a satisfactory period of time. In fact, the recurrences are distributed from a statistical analysis according to chance, and none of the data indicates that recurrence of disease was in any way dependent upon any particular plan of therapy. In addition, two-thirds (18) of those that developed a recurrence, later freely admitted the possibility of reinfection. Of the remaining 9 we have good reason to believe that reinfection was possible in some instances.

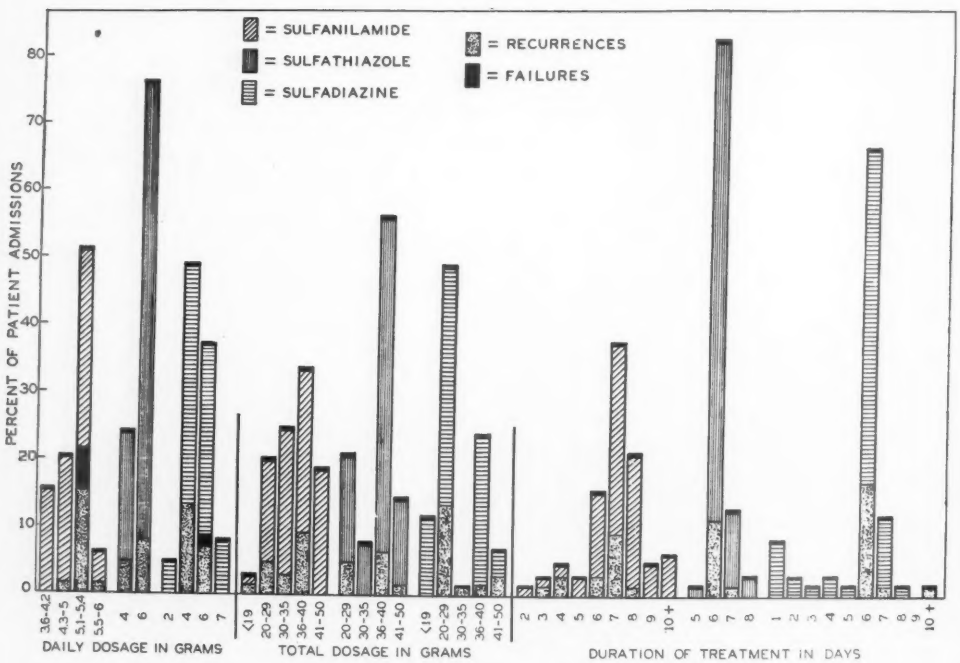

Fig. 7.—Treatment. Daily dosage, total dosage, and duration correlated with recurrence of disease and failures.

On the other hand, in one patient, at least, we feel that reinfection was most unlikely and this recurrence would seem to represent a genuine exacerbation. The patients in the four instances of sulfanilamide failure all received 5.4 Gm. of the drug per day. We feel, at the present time, that if evidence of a satisfactory result is not evident within forty-eight hours, there is little use in continuing the drug in question.

In order to evaluate the specificity of the various compounds we started taking smears and cultures after the lapse of several days. As the sulfanilamide study progressed we shortened this interval in turn, because the first specimen studied was frequently negative, to 48, 24, and 12 hours, respectively. Following the introduction of sulfathiazole

and sulfadiazine, the interval was shortened further so that a considerable number of studies on the secretions were obtained at intervals of two hours after the onset of treatment. The blocks in Fig. 8 illustrate the interval from the onset of treatment to the time of the *first* examination of the secretions. In many instances subsequent studies were carried out at frequent intervals, but this information is not included on the chart. Earlier statements explain why there were not as many observations made early in the sulfanilamide group as there were in the other two groups. The curve on this chart shows the number

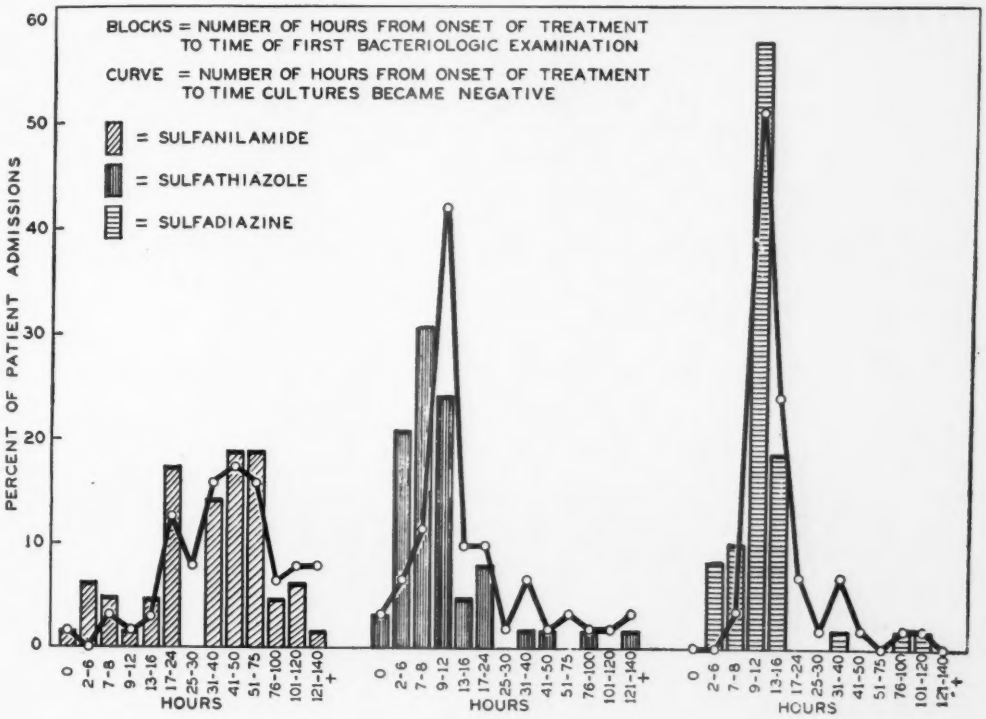

Fig. 8.—Results of treatment.

of hours from the onset of treatment to the time the smears and cultures became negative. Bacteriologic cure is thus seen to be evident most frequently in the sulfanilamide group in forty-one to fifty hours and in the sulfathiazole and sufadiazine groups in nine to twelve hours. Consideration of the data expressed by the curve does not give all desired information because on many occasions the first specimen studied was negative. Obviously then, under those circumstances the exact time of bacteriologic cure was unknown.

For more positive information, Fig. 9 was constructed and illustrates the length of time from the onset of the treatment to the time of the *last* known positive culture. Fifty-nine patients had positive laboratory

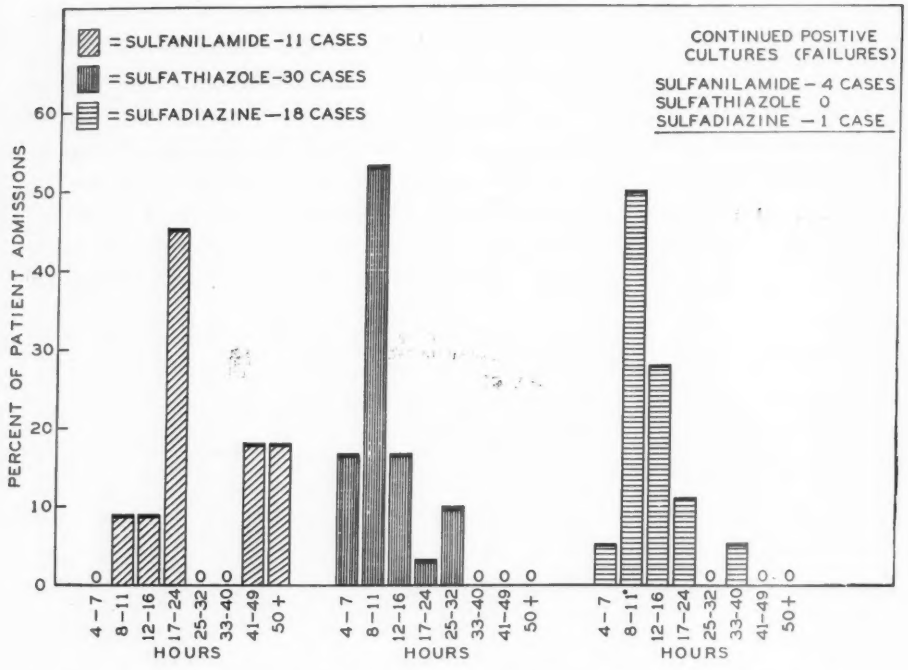

Fig. 9.—Results of treatment. Known positive cultures after onset of treatment.

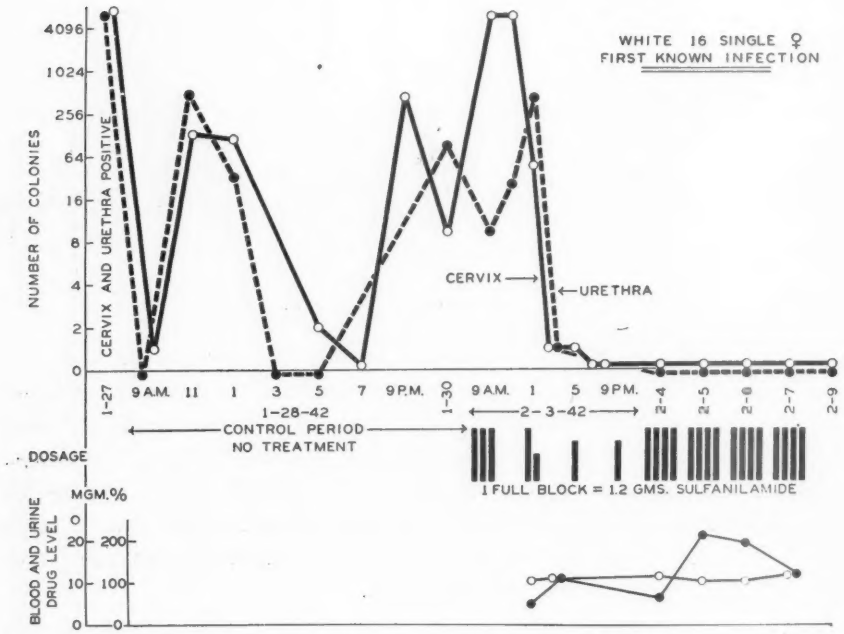

Fig. 10.—Acute gonorrhea treated with sulfanilamide.

tests following the onset of treatment. Eight patients in the sulfanilamide group, 3 of the sulfathiazole group, and 2 of the sulfadiazine group had positive cultures more than twenty-four hours after the onset of treatment. Furthermore, 6 of the sulfanilamide treated cases had positive cultures more than fifty hours after the onset of treatment.

Fig. 10 illustrates graphically the sequence of events in a patient treated with sulfanilamide with reference to gonococcus colony counts on standard unit volumes of secretion obtained from the cervix and the urethra. The number of colonies are represented by figures in a geometrical progression, 4,096 representing infinity as far as quantitative determinations are possible. After the diagnosis was made 7 cultures were obtained at two-hour intervals when no medication was administered, to serve as a control of the effect of repeated cultures on colony counts. Six days later cultures were obtained at the same intervals.

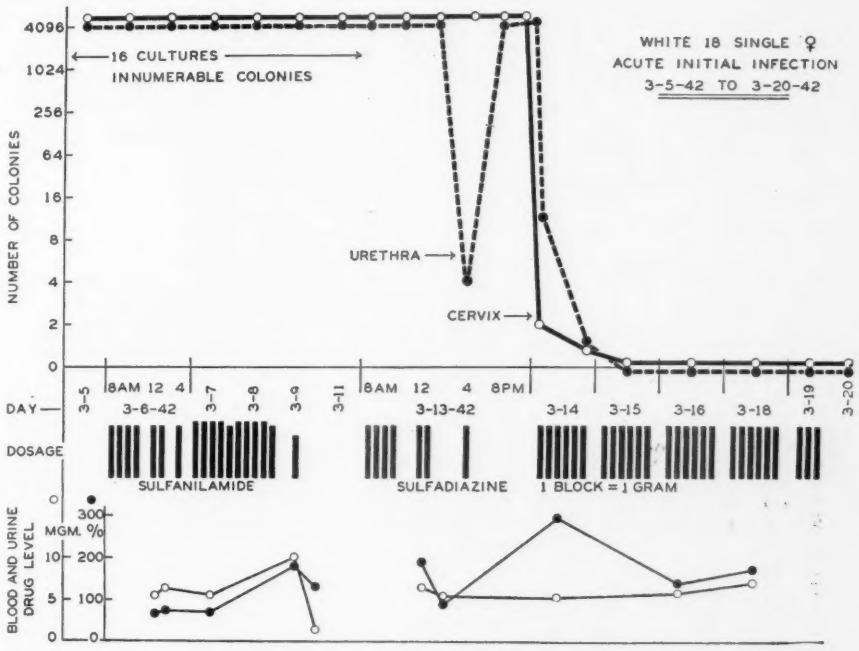

Fig. 11.—Acute gonorrhea treated with sulfanilamide and sulfadiazine.

Sulfanilamide (3.6 Gm.) was administered at the time the first culture was taken and 1.8 Gm. four hours later followed by 0.9 Gm. every four hours thereafter. The colony counts indicate a sudden diminution in the number of gonococcus colonies and the cultures became negative in ten hours. This patient was one of two, in the sulfanilamide group, who developed a bacteriologic cure within such a short period of time. The blood concentration was 11 mg. per cent within four hours after the onset of treatment where it remained remarkably constant until the drug was discontinued five days later.

Fig. 11 is constructed along similar lines, expecting no control period is included. The patient was a single, white girl with what was thought to be an acute initial infection confined to the lower genitourinary tract.

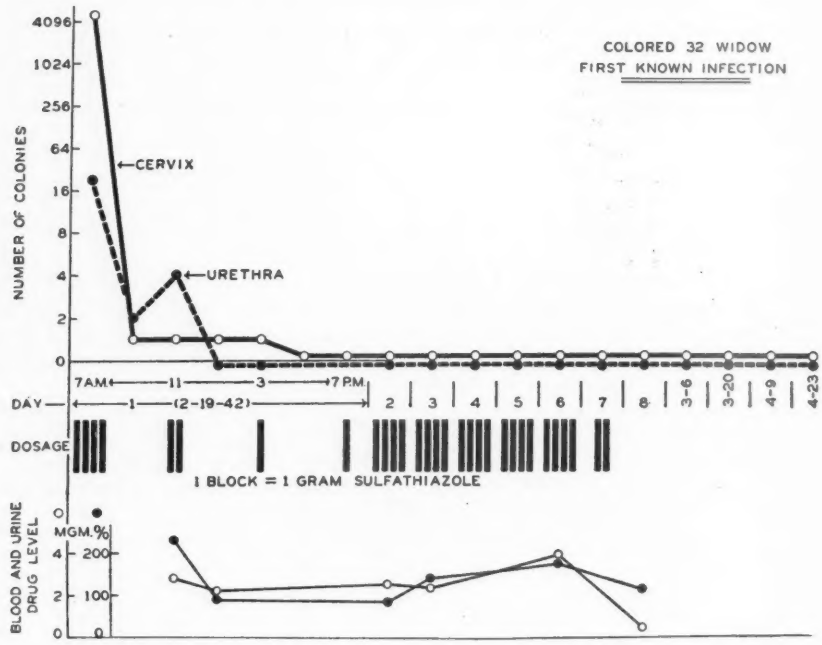

Fig. 12.—Acute gonorrhea treated with sulfathiazole.

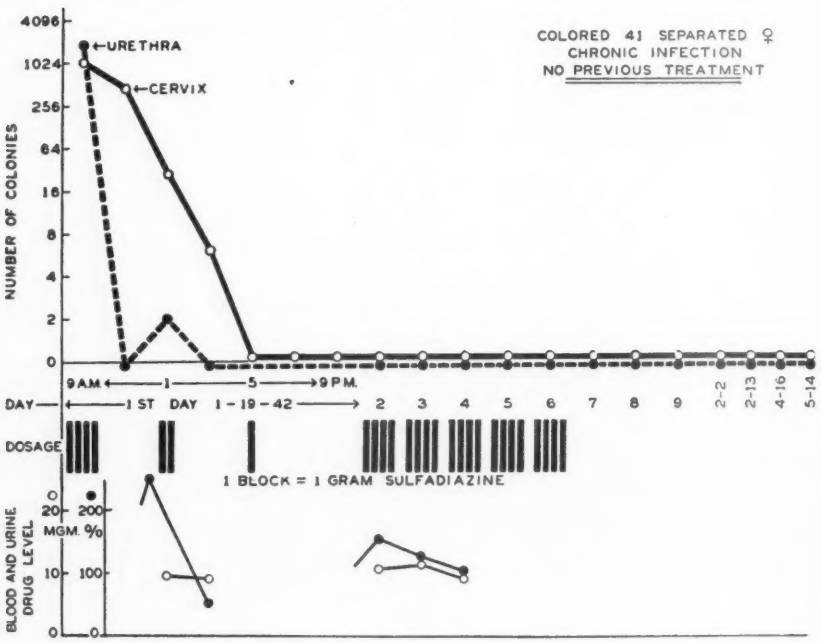

Fig. 13.—Chronic gonorrhea treated with sulfadiazine.

The complete lack of response to the sulfanilamide, however, serves as an adequate control. Many of the infinite colony counts are excluded from the graph because of their similarity. Four days after discontinuing the sulfanilamide, sulfadiazine was started and the same observations made. Cultures thirty-six hours later were still positive which, with the exception of one failure, represents the slowest bacteriologic response observed with this medication. Drug concentrations in the blood were a little lower than usual but we do not believe this factor offers a satisfactory reason for the failure of the sulfanilamide or the slow action of the sulfadiazine.

Fig. 12 represents the course of a 32-year-old widow with a first known infection treated with sulfathiazole. Blood concentrations are lower which is characteristic of this drug. A bacteriologic cure, however, was obtained in ten hours and a significant decrease in the colony count was noted two hours after starting treatment.

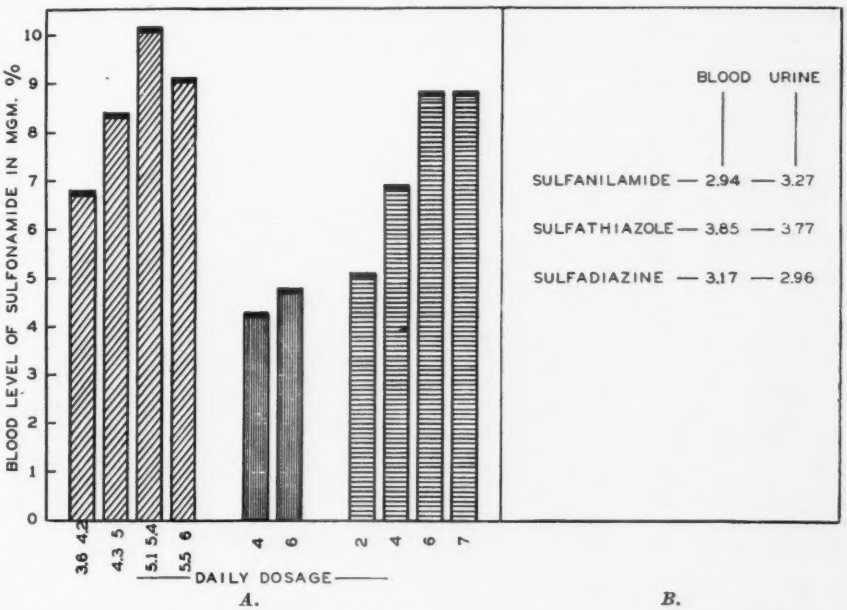

Fig. 14.—*A*, Average highest blood levels of sulfonamide in milligram per cent correlated with daily dosage. *B*, Average number of blood and urine sulfonamide determinations per patient.

Fig. 13 is that of a 41-year-old separated, colored woman with a chronic infection. A bacteriologic cure was established in eight hours following the administration of sulfadiazine. The blood level was 9.6 mg. per cent within four hours after the onset of treatment and was well maintained on a 4 Gm. daily dose. Cultures and smears taken at regular intervals have all been negative and the patient is still under observation.

Fig. 14 illustrates the average number of sulfonamide determinations in the blood and urine in the three groups. The data are based on a total of 591 blood and 441 urine studies. A considerable number of the patients had daily tests performed, while in others tests were done every second or third day during the period of therapy. Many of the tests were carried out before a sulfonamide equilibrium was established while

others were performed after the cessation of administration of the compound and, accordingly, an average of the levels is not particularly illuminating. For this reason, we have plotted in this chart an average of the highest blood levels obtained, in milligrams per cent, for different dosages of the three drugs. In general, it appears that the smaller doses are more efficiently utilized at least as far as availability in an uncombined form is concerned. From a careful review of all of our material we feel that, if necessary, blood and urine determinations could be dispensed with, provided the daily dosage is small (4 Gm. or less), the duration of treatment is short (not over five or six days) and an adequate urinary output is maintained.

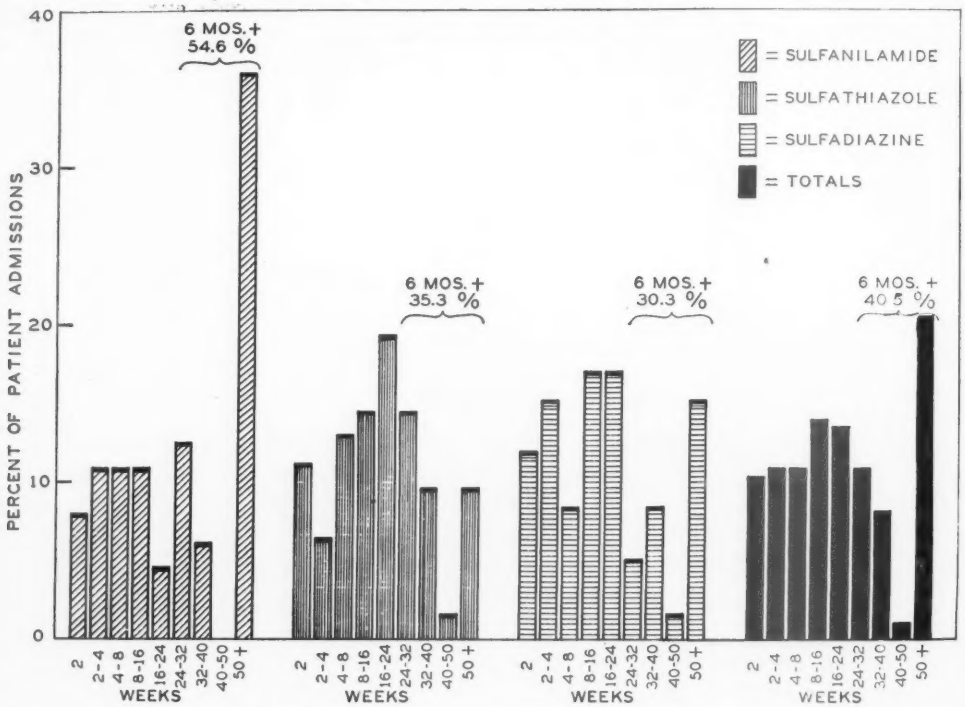

Fig. 15.—Period of follow-up observation.

We have made every effort to obtain a satisfactory period of observation in a special follow-up clinic. Fig. 15 summarizes the length of this interval. Many of the patients are still being observed. However, as of April last it is seen that slightly over 20 per cent were not followed for more than one month, 25 per cent were followed from one to four months while an almost equal number were observed from four to eight months. Slightly more than 20 per cent were kept under observation for one year or longer. In the patients that had recurrence of the disease later the period of follow-up is calculated only to the time of the recurrence. This means the actual period of observation is somewhat longer than is illustrated in this chart. The average number of examinations in the hospital following the onset of treatment was 7.9 and in the follow-up clinic after discharge 3.1 per patient.

Fig. 16 presents in summary the end results. The gonorrheal infection was eliminated from both a clinical and bacteriologic point of view in 180 out of the total of 185 admissions of 158 patients. Five drug failures were observed, 4 being in the sulfanilamide and one in the sulfadiazine group. Three of the sulfanilamide failures promptly responded to one of the other sulfonamides while the other case occurred before these compounds were available and that patient was retained in the hospital until a spontaneous cure developed. The sulfadiazine failure later responded to a second course of the same drug during the puerperium. In 27 instances, there was a later recurrence of the disease. Approximately one-half of these occurred more than four months after treatment. In two-thirds of this group, the possibility of reinfection

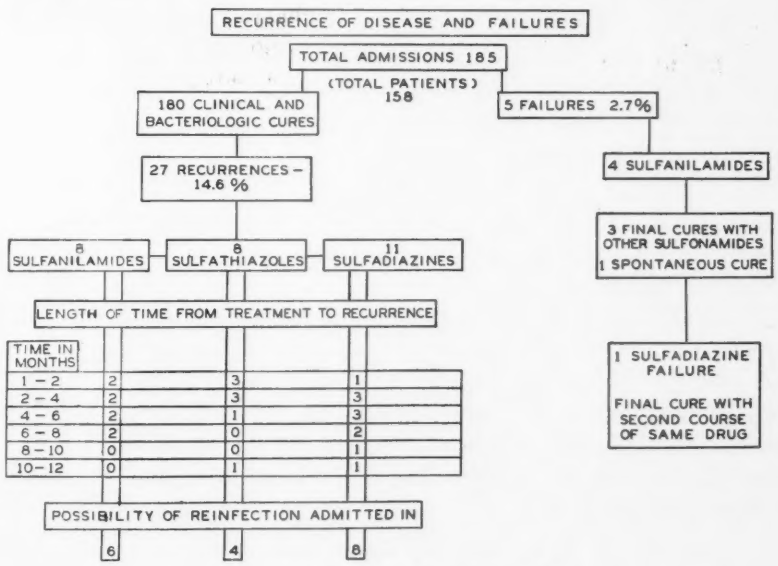

Fig. 16.—Summary of end results.

was admitted, while in the remainder such an admission was not obtained. Obviously, it is impossible for us to say with certainty whether these infections represent an exacerbation of the original infection or whether they are reinfections. Our own feeling, however, is that the great majority at least are new infections.

TOXICITY OF THE DRUGS

Two-thirds of the sulfanilamide group had toxic manifestations, such as nausea, vomiting, anorexia, cyanosis, chills, fever, vertigo, headache, etc., while only 7 of the sulfathiazole and none of the sulfadiazine groups had such findings. Hemoglobin determinations, red and white blood counts, and sedimentation rates were routinely performed at frequent intervals on all patients. The only significant change noted on an analysis of these data was the tendency to develop anemia during sulfanilamide administration. In fact, two patients in this series actually

developed a moderate hemolytic anemia. No such changes were noted in the sulfathiazole or sulfadiazine groups. No significant change in the white cells was noted. Extensive experimental physiologic and pathologic investigations on possible renal lesions following the administration of sulfathiazole and sulfadiazine are being conducted by different workers at the present time. It appears that definite toxic changes not infrequently occur in the kidney of the dog following the administration of sulfadiazine. There is no evidence, however, that such changes take place in man in the dosages referred to and in the presence of good kidney function. There has been no instance of microscopic or gross hematuria nor renal colic such as has been reported by some authors during the administration of sulfadiazine or sulfathiazole. We have not been able to detect any suggestion of renal changes in our patients in this series, and it is our opinion that in the dosage employed, in the absence of any pre-existing renal lesion and if an adequate urinary output is maintained, no real danger exists.

DISCUSSION

It has been difficult to subject our clinical observations to statistical methods of analysis. Leucorrhea and the acute evidence of inflammation in the lower genitourinary tract often subside rapidly. However, where there is a mixed infection at these sites some chronic discharge may persist. It is our impression that acute gonorrheal salpingitis subsides and is cured just as rapidly as is the process in the lower genital tract. It must be made clear, however, that chronic pelvic inflammatory disease and tuboovarian masses caused by other microorganisms are not, in our opinion, affected to even the slightest degree by any of the sulfonamides referred to.

Recently we have been studying the sulfonamide concentration in the cervical secretions for some clue as to why such dramatic results are obtained. Our findings to date indicate much lower concentrations of both sulfathiazole and sulfadiazine than is present in the blood.

Spread of the disease from the lower to the upper genital tract occurred on only two occasions during or following treatment. Both of these patients are included in the failures.

All of our data indicate that sulfanilamide is less specific and slower acting than either sulfathiazole or sulfadiazine. In addition to the previously presented data, we have had the opportunity of observing the results of administering 3.6 Gm. or less per day of sulfanilamide to a few ambulatory patients. The persistence of positive cultures in these cases lends support to the above statement. Another disadvantage to this compound lies in the frequency with which it causes disturbing subjective symptoms. Sulfathiazole and sulfadiazine are almost equally specific. Sulfadiazine is slightly more rapid in its action and causes fewer subjective symptoms.

Occasionally in the control of treatment, smears revealed extracellular gonococci but cultures inoculated from the same exudate failed to grow. Careful investigation of this phenomenon leads us to believe that such forms are nonviable. We have frequently used media for culture containing para-amino-benzoic acid (5 mg. per cent), to inhibit the action of any sulfonamide carried by the inoculum to the media. The results were the same as that obtained were this inhibitor not added. The explanation may be that the exudate actually contains para-amino-benzoic acid, which is very likely so, or that the concentration of the sulfonamide is so weak that it has no effect.

All of our observations indicate that a satisfactory therapeutic response is obtained promptly or not at all. If negative cultures are not obtained within forty-eight hours after the onset of treatment it would appear that there is little use in continuing the treatment, at least with the particular sulfonamide concerned.

Four grams of sulfathiazole or sulfadiazine daily gives just as satisfactory results as does the 6 Gm. daily dosage and, in fact, our most recent but somewhat limited experience indicates that a 2 Gm. daily dose may be often equally efficacious. However, this is not always true and, accordingly, we cannot advise its routine use as has been suggested by many public health agencies. Equally good results were obtained in the cases where 1 Gm. of the drug was given at hourly intervals for seven hours and then the drug entirely discontinued. In the light of these observations, a rational plan of treatment might be 4 Gm. per day in divided doses of either of these compounds for six days. If it were necessary to supervise the administration of the drug, 1 Gm. could be administered every hour for 7 doses. In some respects this latter plan appears more logical than the former but, as yet, we have not had sufficient experience to recommend its general use.

CONCLUSIONS

1. Cultures of cervical, urethral, or other exudates are much superior to reliance on smears alone for the diagnosis, control of treatment, or follow-up observations in the management of patients with gonorrhea.

2. The latent form of the disease is often asymptomatic or associated with leucorrhea only (43 per cent of cases) and, very frequently, cannot be recognized without the aid of cultures.

3. The efficacy of the therapy is unaffected by age, color, pregnancy, duration of disease, or site of infection.

4. Treatment and its control is more efficient if the patient is hospitalized.

5. Of the three drugs employed sulfanilamide is the least specific and the most toxic. Sulfathiazole and sulfadiazine are much more specific and rapid in their action and definitely less toxic. Sulfadiazine appears to be slightly more efficient than sulfathiazole and is the least toxic.

6. Bacteriologic cure is most frequently encountered within nine to twelve hours after the administration of sulfathiazole or sulfadiazine and forty to fifty hours after sulfanilamide.

7. Four grams of sulfadiazine or sulfathiazole in divided daily doses for six consecutive days constitutes, at the present time, the most ideal form of therapy.

8. Bacteriologic cures were established in 180 out of 185 admissions of 158 female patients with gonorrhea. There were 27 recurrences of the disease which were thought, for the most part, to be new infections. There were four failures with sulfanilamide and one with sulfadiazine.

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DISCUSSION

DR. FREDERICK H. FALLS, CHICAGO, ILL.—The use of any agent in the cure of disease must always be evaluated in the light of what may be expected to happen if the disease were allowed to progress untreated or treated by some other method. Dr. Douglas has rightfully pointed out that gonorrhea in the female generative tract is rarely if ever fatal; that a large percentage of the cases are infections of the lower genital tract which tend to die out spontaneously. It is a matter of common knowledge that the same rule holds true for infections of the upper genital tract. The true worth therefore of a given method of treatment for such a disease depends upon the speed with which the results are accomplished, their permanence, and on the innocuousness of the remedy.

The vulnerability of the gonococcus to various therapeutic agents is well recognized, and one must remember that specific fever therapy in this disease antedated Carpenter's work by many years. Vaccines, composed of dead gonococci and mixed bacterial filtrates known as "phylacogen" were used freely as early as 1910. This was followed by milk injections, then the Elliott treatment and more recently by the Newman thermo-flo, all of which have depended on raising the temperature of the tissues to devitalize the gonococcus. Each of these methods produced good results according to their sponsors, but all lack the dramatic speed in attaining a cure reported by the method here under discussion.

I should like to raise the question of the diagnosis of gonorrhea in the female based on the finding of a gram-negative diplococcus by culture from the urethra and cervix. Would we make a diagnosis of pneumonia if we could cultivate the pneumococcus from the nose and throat, or of diphtheria if we found a gram-positive rod that grew well on Loeffler's media in the throat? Should we call every one a typhoid fever patient from whom a typhoid-like bacillus may be cultivated from the stool? I should be in favor of disregarding for the purpose of a study of this kind all cases which did not present a definite history or clinical symptoms or indisputable stigmas of gonorrhea. Not that I would minimize the important implications of this study in demonstrating a larger number of cases which ap-

parently are gonorrheal carriers, but to say that by a certain method we have cured these women of gonorrhea is hardly justifiable.

The second question I would raise is whether the evidence here presented definitely settles the question of cure in a great group of these patients. It certainly shows that when the sulfa content of the blood is raised to a certain level that some of the drug appears in the cervical and urethral secretions and that under these circumstances the organisms previously cultivated from these surfaces could no longer be made to grow. It would seem that the organism might be inhibited from growing by the drug without being killed, and that unless all of these cases were followed up by culture, after all therapy had been stopped and the blood level of sulfathiazole had returned to normal, that the possibility of revival of the organism under the more favorable conditions might be expected. This might account for some of the recurrences here cited as potential reinfections. It would also have been more convincing if all of the gram-negative diplococci isolated by culture had been subcultured and their carbohydrate fermentation reactions studied in order to prove their right to be designated gonococci.

The susceptibility of this organism to sulfa drugs can be shown by an accidental circumstance which occurred a few weeks ago at the University of Illinois. A class in bacteriology was given some human blood to make up blood agar plates. The plates were inoculated with live cultures but no growth obtained on incubations. Subsequent investigation showed that the blood had been taken from a patient who was under treatment with a sulfa drug.

The results of the study of 100 cases of acute salpingitis at Cook County Hospital with a comparison of patients treated with sulfanilamide, and those not receiving the drug are as follows:

Patients receiving sulfanilamide:	
Average stay in hospital	11.23 days
Average days of temperature	6.64 days
Average time sick	17.83 days
Patients *not* receiving sulfa drugs:	
Average stay in hospital	11.03 days
Average days of temperature	6.80 days
Average time sick	20.48 days

The patients with the sulfa drug received at least 240 gr. while being treated. The highest amount given was 1,200 gr. while being treated.

DR. FRED L. ADAIR, CHICAGO, ILL.—For a number of years past Dr. Hesseltine, Dr. Lucile Hac, and I have been studying patients, principally ambulatory, secured through the Social Hygiene Clinic in Chicago. Naturally the patients did not report unless they had some symptoms. We were unable to follow them closely within a few hours after treatment. I think, however, we can draw some conclusions from this series of over 480 women and some children who were treated.

With the different sulfa drugs, we have in the main drawn about the same conclusions as Dr. Douglas. Certain differences in the blood level of these drugs may be obtained in relation to the dosage. For instance, with the sulfathiazole we had a blood level of 2 to 3 mg. per cent; with sulfadiazine we had a level of 4 to 6 mg. per cent, and with an increased dosage of the sulfadiazine we had as high as 11 mg. per cent with 3 Gm. doses.

We rely much more on cultures than we do on smears for diagnosis as well as for the criterion of cure. With sulfadiazine, we had 98 per cent negative cultures within four days; with sulfathiazole, we had 97 per cent; with sulfapyridine, 93 per cent; and with sulfanilamide, 88 per cent negative cultures.

As a criterion of cure we have used the silver nitrate method, but we have found that menstruation is probably the best provocative test. We run our cases through

two menstrual periods with negative smears and cultures before they are pronounced cured.

Sulfanilamide should not be used in children, partly because of its toxicity and also because in children it tends to produce drug-fast strains. Sulfathiazole appears to be the drug of choice in the treatment of children, although we have not treated a sufficient number to draw final conclusions. In some instances in children, we supplemented sulfonamide therapy with stilbestrol in order to obtain a cure.

The sulfathiazole and sulfadiazine are the drugs of choice in the treatment of women. The rate of cure with sulfadiazine was 95.8 per cent. The women respond rapidly to the sulfonamides and become noncontagious earlier than when local treatment is used. Secondary complications are rare when the sulfonamide therapy is administered early. Drug-fast strains were noted in only 1 in 354 patients.

DR. CHARLES C. NORRIS, PHILADELPHIA, PA.—In the gonorrhea clinic at the University of Pennsylvania 158 cases, almost all of whom are adults, have been treated with sulfathiazole during the past year. Eighty per cent of these cases were in the chronic stage. One of our outstanding conclusions is that very little can be determined by clinical diagnosis in the chronic cases. So many women have suggestive signs who do not prove to have gonorrhea culturally, while so many positive cases occur in which the stigmas are inconclusive or absent. We concluded also that cultures were twice as reliable as other methods, including smears.

Nearly all of our cases were studied for three months. We had about the same number of negative cultures within the first week as has been reported. In the cases that were studied for three months, however, we had 17 per cent of recurrences and of this number the large majority were cleared up by the second course of treatment. However, there were a few cases among that group which seemed to be very difficult and did not respond to a second course of treatment. Of course, those cases may possibly be due to reinfection which is not admitted by the patients. We had few reactions. Treatment with sulfathiazole is the best method of treating gonorrhea in the lower genital tract of women, and I believe has some value in the treatment of gonococcal pelvic inflammatory disease.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—I believe that this subject must be looked at from another point of view than the purely clinical one and that we should give some attention to the public health aspects in question. In that connection I do not believe that we should accept without some question the entirely enthusiastic reports which have been brought forward with respect to the treatment of gonorrhea by the sulfa group of drugs. These enthusiastic reports have led in one instance that I know of, and there may be others, to the publicity by public health agencies about the unfailing value of the sulfanilamide group in the treatment of gonorrheal infection. In fact, in the particular instance of which I speak, a certain department of health was ready to post in public conveyances a notice to the effect that gonorrhea could be cured by sulfathiazole, and the group backing this proposition went so far as desirous of publicizing the fact that the public should be informed about the value of these drugs to the same degree that they have been already informed about the value of quinine in the treatment of malaria. In other words, that any person suspecting they have an infection or having been told that they have a gonorrheal infection, might go to any corner drugstore and buy a box of sulfathiazole tablets for self administration.

Our Society, to which this excellent study has been presented, need not perhaps pay much attention to the matter. However, the outcome of such presentations may be that, getting into the hands of public health officers and others who are concerned with the reduction of these venereal diseases, the resultant effect may prove unfortunate. I do not believe that it is desirable for the public at large to

be told that gonorrhea is an easily curable disease, whether in men or women. I am afraid that such an attitude might contribute to the further dissemination of a disease which now constitutes a menace to our Armed and Defense Forces. In the present war emergency every effort is being made to reduce the incidence of venereal disease. I do not feel that it would be desirable that people should be misled by the claim that gonorrhea can be cured easily and without satisfactory medical oversight and control.

DR. DOUGLAS (closing).—In discussing this subject we must clearly differentiate chronic pelvic infections with associated inflammatory masses from gonorrhea. The former condition is not in our experience favorably affected by any of the sulfonamides that have been employed. On the other hand, if a therapeutic response is not obtained in the treatment of gonorrhea within forty-eight hours, consideration should be given to changing the compound or stopping its administration.

Reference has been made to the production of an asymptomatic carrier state. We have encountered this phenomenon with the smaller dosages of sulfanilamide but to the best of our knowledge we have not encountered the condition following the administration of sulfathiazole or sulfadiazine. However, we believe this possibility is one reason why the daily dosage should not be too low.

Dr. Falls has referred to heat therapy. The treatment introduced by Carpenter was based on the thermal death time of the infecting strain of gonococcus. In order for a cure to follow, the body temperature should be raised to 41.5° C. as long or longer than this period of time. Other forms of heat treatment where this temperature is not reached or maintained for the indicated time does not constitute specific fever therapy as I have employed the term.

The question has been raised regarding the identification of the strains isolated. Sugar fermentation reactions were frequently employed and the oxidase reagent was routinely used. The asymptomatic patients referred to were sent to us for treatment by the Department of Health of New York City. They had already disseminated the disease.

I may say that the time required for the cultures to become negative after the onset of treatment has been the subject of thorough investigation. We have employed p-amino-benzoic acid in our media to nullify the effect of any sulfonamide carried in the secretions to the media. Determination of the concentration of the drug in the cervical secretions has also been carried out on many occasions. As a result of these studies we are forced to conclude that the reported results are correct. It may be that this form of treatment is more specific in the female than in the male.

Public Health agencies already have the information and are widely disseminating it. In many instances they advocate a 2 Gm. daily dosage which we believe to be effective usually, although not always. For this reason we believe the 4 Gm. daily dosage more desirable.

We would prefer to be less enthusiastic but our results hardly justify such a position. The term "cure" as employed is modified by "bacteriologic" when based on laboratory data and "apparent" when determined by clinical findings.

STUDIES OF THE HUMAN CORPUS LUTEUM*

Evidence for the Early Onset of Regression of the Corpus Luteum of Menstruation

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(From the Department of Gynecology and the Henry Baird Favill Laboratory of St. Luke's Hospital, and the Department of Obstetrics and Gynecology of Northwestern University Medical School)

THE subject of this report is concerned with the time at which regression begins in the corpus luteum of menstruation.

The life cycle of the corpus luteum of menstruation in the human being has been described and its division into four typical stages has been universally accepted. These stages are termed proliferation, vascularization, mature or blossom stage, and stage of regression (Meyer, 1911; Frank, 1914). Meyer (1911 and 1932) observed that the blossom and regression stages were imperfectly limited and stated that the beginning of regression could not be definitely recognized. Novak (1934 and 1941) stated that regression begins shortly before the onset of menstruation, about the twenty-sixth day in a patient with a twenty-eight-day ovulatory cycle. The material to be presented here indicates rather that regression begins at the termination of the so-called vascularization stage, four to six days before the onset of menstruation.

In order to avoid confusion, I wish to state that I shall not describe the reported specimens in relation to days of the menstrual cycle. The variability in the length of normal cycles is so great that the dating of specimens according to this method may lead to confusion. Since that portion of the menstrual cycle between the time of ovulation and the onset of menstruation is relatively constant, I shall date all specimens by the probable days of age of the corpus luteum. Exact age of a given corpus luteum is difficult to determine. Histologic characteristics offer the best method. It is possible to evaluate the approximate age within two to three days by these histologic characteristics. For the most exact age determinations, it is necessary to study a series of specimens in this report. By this method of comparison the age of an individual specimen can be estimated more accurately. The study of the normal endometrium is also an aid in making age determinations of corpora lutea.

MATERIAL AND METHODS

The 97 specimens studied were obtained from patients undergoing pelvic operations by members of the gynecologic department of St. Luke's Hospital, to whom I express my appreciation. The patients were in active menstrual life and the menstrual cycles were normal. The

*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

patients were operated upon because of pelvic pathology, such as fibroids, endometriosis, or residues of pelvic infection. That the corpora lutea and endometriums can be normal under such circumstances has been shown by Sammartino and Gandolfo Herrera (1940), and Brewer and Jones (1941). Thus these specimens are considered to be normal. The entire corpus luteum was obtained in each instance. The associated endometrium was obtained in all but ten instances. Those specimens on which chemical analyses of the lipid content were made were quickly weighed and one-half of each was taken for cytologic study and half for chemical analysis. Fixation in all instances was begun within ten minutes after the tissues had been removed from their blood supply. Fixation in the various solutions was carried out in the refrigerator in order to retard the changes that occur in tissues after removal from their blood supply. The fixations used were aqueous-formol-chrome-sublimate, osmication after the preceding fixation, and neutral formalin.

Of the 97 corpora lutea studied 13 were in the proliferation stage, 31 in the vascularization stage, 36 in the so-called mature or blossom stage, and 17 in the so-called stage of regression after the onset of menstruation. In addition, 8 corpora lutea of early pregnancy were studied.

THE VASCULARITY OF THE CORPUS LUTEUM

The youngest specimen, approximately twenty-four hours old, has small capillaries extending into the granulosa cell layer. The growth of the capillaries is rapid as indicated by the numerous endothelial cells undergoing mitotic division. In specimens three days of age capillaries extend completely through the granulosa cell layer and project into the central cavity. The majority of the capillaries are distended with blood. Extravascular blood is marked throughout the entire cell layer, and in some regions small lakes are formed. The entire picture during these first three days of life of the corpus luteum is one of rapid and extensive vascularization of the granulosa lutein cell layer.

During the subsequent five or six days of life of the corpus luteum, which in the literature is termed the vascularization stage, the development of the vascular system reaches its peak. In corpora lutea five days of age, the tortuous capillaries are arranged in such a manner that they are immediately adjacent to most of the granulosa lutein cells. Each vessel is distended with blood (Fig. 1). In specimens of this age there is little extravascular blood in the granulosa lutein layer. There is an ingrowth of connective tissue along with the capillaries. This tissue, in conjunction with the vascular elements, projects into the central cavity, and during the next few days of life, the corpus luteum forms a lining separating the granulosa lutein cells from the central cavity. Until the corpus luteum is approximately seven to eight days of age the vessels throughout the granulosa lutein layer are filled with blood.

In specimens eight to ten days of age, there is a gradual diminution of the amount of blood within the vessels located in the granulosa lutein layer. The capillaries are more narrow and more straight (Fig. 2). Only a few capillaries in occasional isolated regions are dilated and filled with blood. There is little or no extravascular blood in the granulosa lutein cell layer. In the connective tissue core, however, the vessels are all dilated and filled with blood. There is also an increase in the amount of extravascular blood in this core.

In corpora lutea after the tenth day of life, there is little blood either within or without the vessels in the granulosa lutein layer (Fig.

3). Only an occasional capillary is found which contains any blood. They are for the most part collapsed. There is also a marked increase in the amount of connective tissue surrounding the vessels.

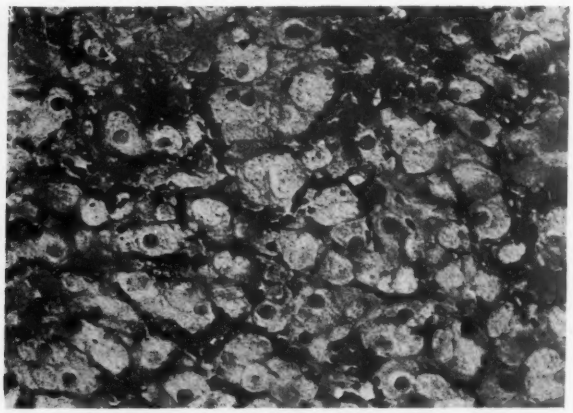

Fig. 1.—The vessels in the granulosa lutein layer are distended with blood (blood appears black in photomicrograph). The capillaries are arranged immediately adjacent to most of the granulosa lutein cells. There is some extravasation in this layer. ×345.5. Patient 342, aged 46 years. Menstrual cycle twenty-eight to thirty days with four to five day flow. Specimen removed on eighteenth day of cycle. Estimated age of the corpus luteum is approximately five days.

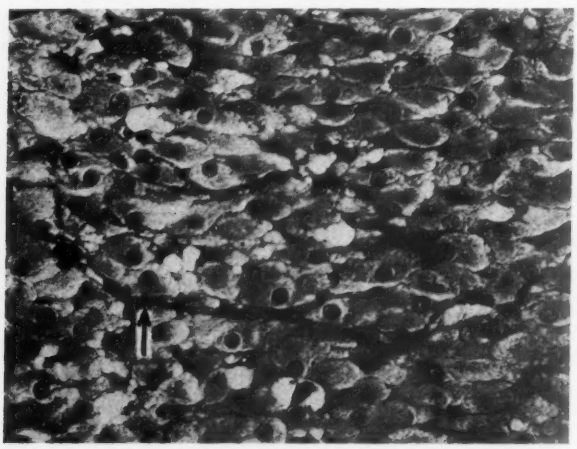

Fig. 2.—The vessels in the granulosa lutein layer are straight, narrow, and contain little blood (arrow). In many regions all the vessels are collapsed and empty. ×345.5. Patient 337, aged 42 years. Menstrual cycles twenty-eight days in length. Flow lasts four to five days. Specimen removed on the twenty-first day of the cycle. Estimated age of the corpus luteum is approximately nine days.

The cessation of development of the vascular system throughout the granulosa lutein layer, the reduction in the blood in the vessels, the marked narrowness and straightness of the vessels, the collapsed capillaries, and the great increase in the amount of connective tissue surrounding the vessels are interpreted as evidence of regression of the vascular system. These changes begin to appear at about the eighth day of life of the corpus luteum.

In corpora lutea of early pregnancy, the above-described changes do not take place. There is instead a continuation of the development and functioning of the vascular system.

A review of the many descriptions of the vascularization stage of the human corpus luteum, as well as the findings reported here, indicate that a reduction in vascularity of the corpus luteum occurs at the end of the vascularization stage. During the so-called blossom stage all authors describe a marked reduction in the amount of blood in the granulosa lutein layer and regressive changes in the vascular system. According to this there is, during the previously so-called period of maximum function, a marked decrease in vascularity. This is not consistent with the known fact that for maximum function of any tissue, a maximum blood supply is required.

It is more sound to conclude, first, that the period of maximum function of the corpus luteum coincides with the period of greatest vascularity, which, in this instance, is the so-called vascularization stage;

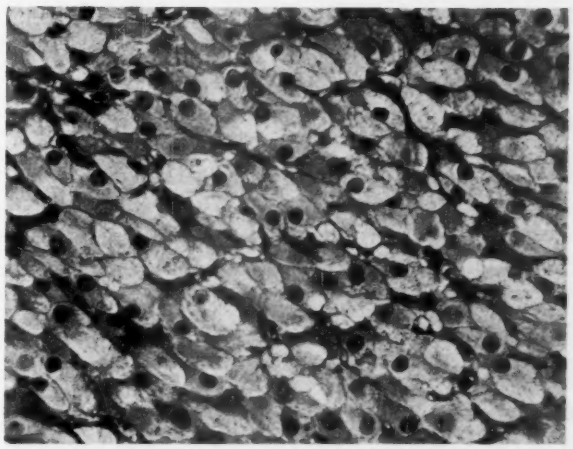

Fig. 3.—This corpus luteum, approximately eleven days of age, was removed on the twentieth day of the cycle. The capillaries are collapsed and empty. ×345.5. The patient, No. 345, was 46 years of age. The menstrual cycles were twenty-eight days in length and the flow lasted three to five days.

and second, that when there is a decrease in the vascularity of the corpus luteum there is a simultaneous decrease in functional activity of that gland. It follows then, that the function of the human corpus luteum of menstruation begins to decrease at the termination of the vascularization stage. The reduced vascularity and the regressive changes of the vascular system during the period of life of the corpus luteum that has been called the blossom, or mature stage indicates, in reality, that this is the period of beginning regression of the gland.

THE GRANULOSA LUTEIN CELLS

The changes in the granulosa lutein cells that indicate functional activity appear simultaneously with the ingrowth of capillaries into that layer. With the steady increase in vascularity, the cells become larger and acquire mature functional characteristics. In corpora lutea approximately seven to eight days of age all of the granulosa lutein cells are not developed to the same degree as Meyer (1911 and 1932) has previously reported. In this stage, the cells contain many small lipid drop-

lets scattered through the cytoplasm. The greatest lipid content is observed in those cells along the border of the central cavity. The nuclei are large, vesicular, and round or oval.

Near the end of the vascularization stage (corpora lutea eight to nine days of age) some of the granulosa lutein cells begin to degenerate. In a typical specimen of this age group (No. 337) approximately nine days of age, there are rather frequent granulosa lutein cells that are large, have clear cytoplasm, and pyknotic nuclei (Fig. 4). The endometrium associated with this corpus luteum shows no evidence of regression. In specimens of this age group some lipid laden cells have nuclei that are pyknotic, while in others the nuclei are nearly normal. In later stages, the number of cells evidencing degeneration increases progressively. In Specimen 255, approximately eleven days of age, such

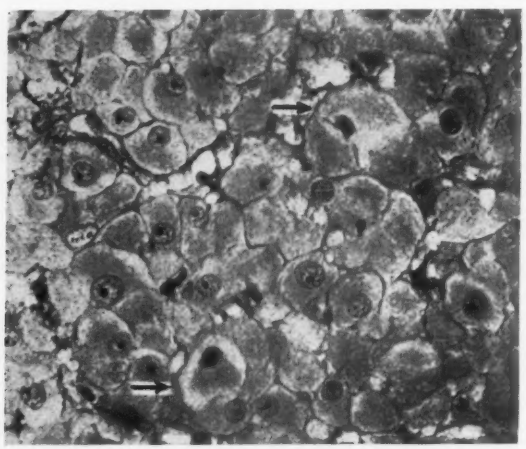

Fig. 4.—Near the end of the vascularization stage there are in the granulosa lutein layer large degenerating cells with clear cytoplasm and pyknotic nuclei. Two are shown here (arrows) ×491. This corpus luteum, aged 9 days, was removed on the twenty-first day of the cycle. The patient, No. 337, aged 42 years, had cycles of twenty-eight days in length with four or five days' flow.

degenerating cells are more numerous and a greater number of nuclei are pyknotic (Fig. 5). These more extensive zones of degeneration are localized. The amount of lipid in most of the granulosa lutein cells is increased, and the droplets are larger. The endometrium of this specimen is shown in Fig. 6. Involution has begun as indicated by the squashed appearance of the glands and the absence of edema. Superficial infiltration of leucocytes and lymphocytes has not yet occurred.

During the eighth to the tenth day of life of the corpus luteum, many of the granulosa lutein cells continue to enlarge somewhat. Some of these cells are larger because of degenerative changes with an increase in the number and size of lipid droplets, while some are larger probably because of a continuation of their secretory function. From the eleventh or twelfth day on, however, the vast majority of all granulosa lutein cells shrink in size. In Specimen 149, which is typical of those approximately thirteen days of age, there are many large degenerating granulosa lutein cells. In addition, many cells are shrunken and have intact nuclei. Other shrunken cells have nuclei that are irregular in shape, stain poorly, and are variable in size (Fig. 7). The cytoplasm in these cells is vacuolated. The cell membranes are irregular. The visible lipid material

in increased. The endometrium is shown in Fig. 8. Involution has taken place, and there is some infiltration of leucocytes and lymphocytes superficially.

In corpora lutea removed just before the onset of menstruation (approximately fourteen days of age), the vast majority of the granulosa lutein cells are shrunken. Many retain intact nuclei. In Specimen 406,

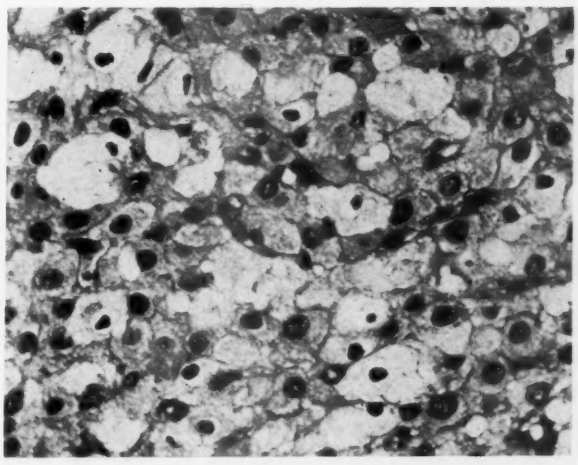

Fig. 5.—Degenerating granulosa lutein cells are numerous. There is no blood in the vessels of the granulosa lutein layer of this specimen. ×491. The estimated age is approximately twelve days. The endometrium undergoing involution is shown in Fig. 6. This specimen was obtained from Patient 255, aged 35 years, on the twenty-seventh day of the cycle. The cycles were twenty-six to thirty-five days in length with five days' flow.

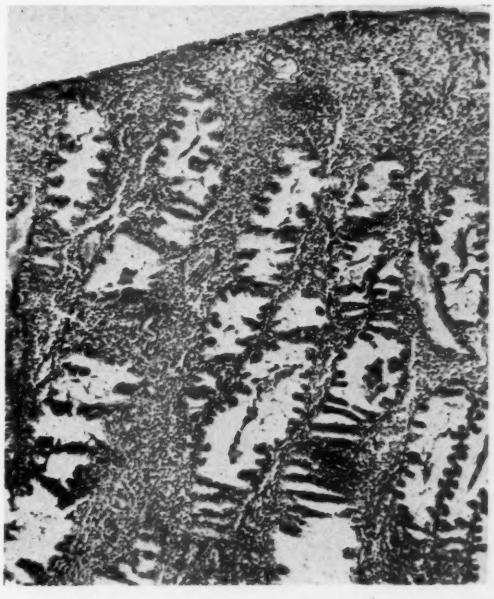

Fig. 6.—Involution in this endometrium has occurred as indicated by the squashed appearance of the glands and the loss of edema fluid. The regressing corpus luteum is shown in Fig. 5.

removed within six hours after the onset of menstruation, the cells are small; the nuclei are indistinct; the lipid content is increased; and the staining quality of the nuclei and cytoplasm is poor (Fig. 9). Most of the endometrium is still intact although the characteristic premenstrual loosening up of the tissue is apparent (Fig. 10). In the progressing

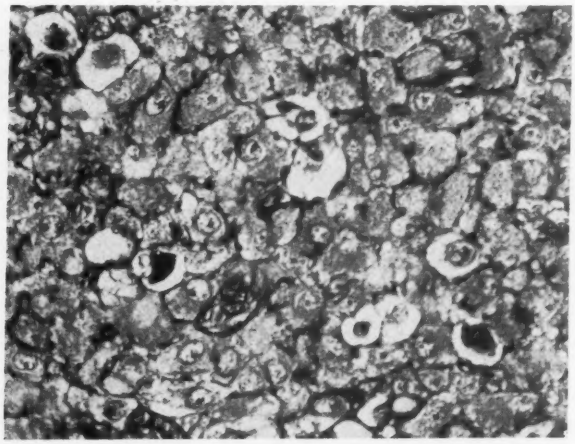

Fig. 7.—In this degenerating corpus luteum approximately thirteen days of age, the granulosa lutein cells are shrunken. Numerous cells have pyknotic nuclei and clear cytoplasm. The cell membranes are irregular and the connective tissue is increased. ×491. The endometrium is shown in Fig. 8. The patient, No. 149, aged 36 years, was operated upon on the thirtieth day of her cycle. Her cycles were usually twenty-eight days in length with three or four days' flow.

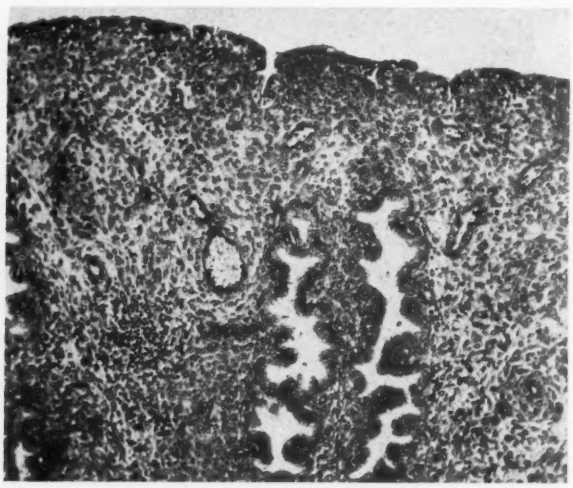

Fig. 8.—This photomicrograph shows the infiltration of leucocytes and lymphocytes that usually occurs two to three days before menstruation. The corpus luteum is shown in Fig. 7.

stages of death these changes in the corpus luteum are more profound. The cell membranes are finally lost and connective tissue replaces the granulosa lutein layer. Connective tissue invasion of the granulosa lutein layer is a continuous process from the time of ovulation. During regression of the gland, however, the invasion is more rapid.

The degenerative changes that characterize regression of the corpus luteum are fatty degeneration and simple atrophy of the granulosa lutein cells.

At about the eighth or ninth day a marked increase in visible lipids in the granulosa lutein cells is observed. During the subsequent existence

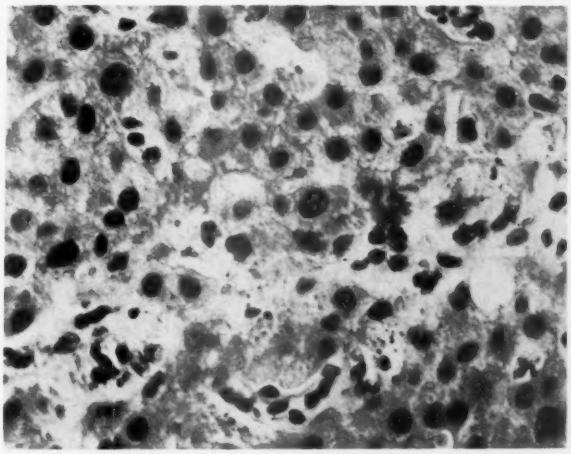

Fig. 9.—In this photomicrograph of the granulosa lutein layer of a specimen removed six hours after the onset of menstruation, the general staining qualities of the cells are markedly reduced, the cell membranes are indistinct, and the nuclei evidence pyknosis and karyorrhexis. ×491. This patient, No. 406, aged 45 years, had cycles usually of thirty days with five or six days' flow. This cycle just completed was thirty-one days in length. A portion of the endometrium which has not yet desquamated is shown in Fig. 10.

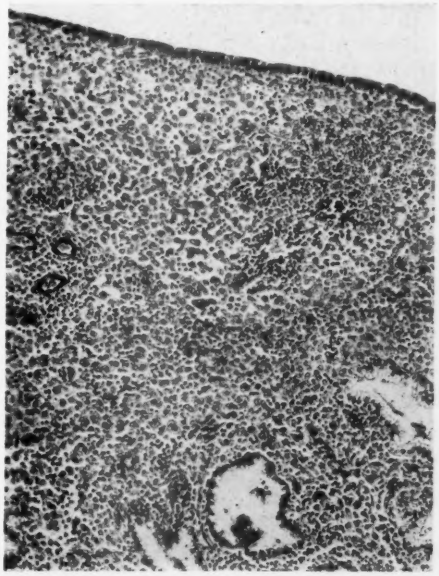

Fig. 10.—This photomicrograph shows the loosening up of the stroma, the loss of edema, the collapsed glands, the infiltration of leucocytes and lymphocytes, and the extravasation which indicate impending menstrual slough. Desquamation has occurred in other portions. Menstruation began clinically six hours before operation. The corpus luteum is shown in Fig. 9.

of the corpus luteum, the lipid content increases. That the increase of lipid content is a part of a degenerative rather than a functional process is suggested by four things. First, the quantity of lipids increases steadily throughout the subsequent degeneration of the corpus luteum. Second, the lipids are most abundant in those cells showing histologic evidence of degeneration. Third, the lipid droplets are of various sizes and many are large globules in contrast to the fine droplets observed in earlier functional stages. Fourth, in the presence of continued or increased functional activity of the corpus luteum, such as occurs in pregnancy, no such increase in visible lipids occurs. In the granulosa lutein layer the simultaneous occurrence of fatty degeneration and reduced circulation suggests that the fatty changes are the result of anoxemia.

Simple atrophy is recognizable in the granulosa lutein cells of corpora lutea from eleven days of age on (Figs. 5, 7, and 9). This degenerative process, since it is a gradual one, may be assumed to have begun at least a day or two before the atrophic cells can be positively identified. This is necessarily true, since it is difficult to discern an actual reduction in the size of granulosa lutein cells because at the onset of degeneration the number of cells so involved is few. Furthermore, the marked irregularity and the characteristic jumbled arrangement of the lutein cells, and the plane of section in which the cells must unavoidably be cut adds to the difficulty of interpretation. It is only when a sufficient number of cells has undergone a sufficient degree of atrophy that this type of degeneration can be unequivocally demonstrated. As noted above, this can be done from the eleventh day of age of a corpus luteum on. Simple atrophy of the granulosa lutein cells is undoubtedly the result of anoxemia.

The progressive character of the degenerative changes in the granulosa lutein cells after the eighth day and the fact that if pregnancy intervenes such degenerative changes are at a minimum suggests that regression begins at the termination of the vascularization stage.

The observations on the associated endometriums demonstrate that regressive changes in the endometrium appear later in the cycle than do the regressive changes in the corpus luteum. This is due to the fact that there is a lag in the endometrial response both to corpus luteum stimulation and to the withdrawal of that stimulation. The regressive changes in the endometrium are observed here approximately four days before the onset of menstrual flow. Regression of the corpus luteum then must begin five or six days prior to menstruation, which time corresponds to the termination of the vascularization stage.

PHOSPHOLIPID AND CHOLESTEROL ESTER DETERMINATIONS

Chemical analyses were made by S. Weinhouse on 61 of the human corpora lutea in this presentation. Some of these specimens were not included in the previous report by Weinhouse and Brewer (1942). The chemical methods employed permitted the determination of exact values of the various lipids occuring in each individual specimen.

There is a gradual, steady increase in the phospholipid content from the time just after ovulation to about the tenth day of age of the corpus luteum (Fig. 11). The maximum value is 2 per cent of the fresh moist tissue. From the tenth day of life on there is a decline in the phospholipid content. On the basis of the established fact that the phospholipid content varies directly with the functional activity

of the tissue, it is concluded that the functional activity of the corpus luteum of menstruation reaches its maximum by the eighth or tenth day of its life. After this time, the decline of phospholipid values indicates a decrease in functional activity. In instances of pregnancy, the phospholipid values are increased in association with the increased functional activity of the corpus luteum.

During the first ten days of life of the corpus luteum, there is a slight decline in the cholesterol esters (Fig. 11). After the tenth day there is an abrupt increase. Near the onset of menstruation and after menstruation has started the increase of cholesterol esters is marked.

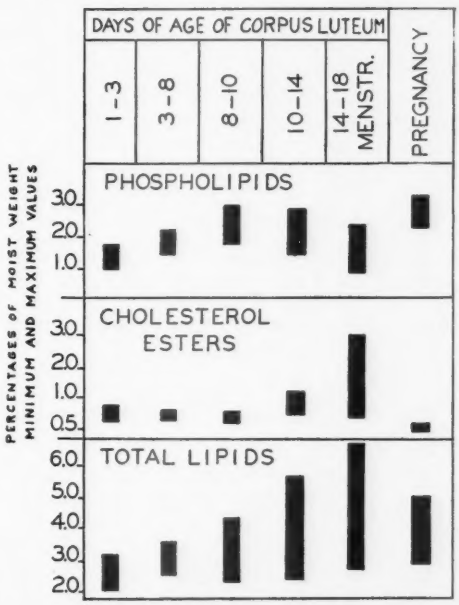

Fig. 11.—*a*, The phospholipid content increases until the tenth day after ovulation, after which it declines. In pregnancy the high phospholipid values indicate a greater degree of corpus luteum function. *b*, The cholesterol ester content remains low until the tenth day, after which it increases abruptly. In instances of pregnancy the minimal values obtained indicate continued functional activity. *c*, The total lipids increase constantly in corpora lutea of menstruation reaching the highest values in later stages of regression. The increase after the tenth day of life of the corpus luteum is the direct result of the increase in cholesterol ester content.

Since cholesterol esters increase in a degenerating tissue, it is concluded that the corpus luteum begins to regress about the ninth or tenth day of its life, and that it degenerates rapidly near the time of, during, and after menstruation. If pregnancy occurs and the gland does not degenerate, the values for cholesterol esters are minimal.

Thus, the chemical evidence suggests that the peak of corpus luteum function is reached during the vascularization stage and that degeneration begins at the termination of this stage.

SUMMARY AND CONCLUSIONS

During the first eight days of life of the corpus luteum of menstruation, there is a gradual increase in its functional activity. By the eighth to the tenth day all the evidence indicates that the peak of functional activity is reached. It is during this first eight to ten days

of life that the essential purpose of the corpus luteum of menstruation is carried out; namely, the preparation of the endometrium for implantation of the fertilized ovum. It is logical to postulate that the maximum function of the corpus luteum of menstruation would endure during this most essential period of its life. Greatest functional activity during this period is indicated by all the findings described in this report. This period of life of the corpus luteum has in the past been termed the vascularization stage. It might preferably be termed the period of essential function of the corpus luteum of menstruation.

If pregnancy occurs, the corpus luteum hormonal activity continues, and is undoubtedly greater than that which exists in a nonfertile cycle. This is indicated by several facts. In early pregnancy there is an increase in the vascularity of the corpus luteum. Fatty degeneration and degeneration by simple atrophy of the granulosa lutein cells are not features of copora lutea of early pregnancy. Corpora lutea of early pregnancy have a high phospholipid content, and a minimal content of cholesterol esters. Greatest quantities of pregnanediol in the urine are obtained during pregnancy (Venning and Browne, 1937; Wilson, Randall, and Osterberg, 1939; Müller, 1940). The marked vascular and secretory development of the decidua vera also denote continued and greater corpus luteum stimulation.

If implantation does not occur by approximately the eighth day after ovulation, this particular ovulatory cycle will be a nonfertile one, since implantation, if it is to occur, takes place by this time (Rock, 1942). It is logical to assume that regression of the corpus luteum will begin at this time, since in the absence of fertilization and implantation, there is no further need for continued corpus luteum function.

It is true, as all the findings demonstrate, that some degree of functional activity of the corpus luteum is maintained after the eighth or tenth day of its life. This is due to the fact that all of the cells do not begin to degenerate simultaneously and that the rate at which degeneration progresses varies in the different cells. Those cells that are not involved, or are only partially involved in the degenerating processes, continue to function. Since they are mature cells, they undoubtedly function efficiently. As a consequence, fewer cells are required to maintain the corpus luteum functional activity at a high level. The functional activity of the gland is reduced only when a sufficient number of cells has undergone a sufficient degree of degeneration. Definite reduction of functional activity can be recognized by the tenth or eleventh day of age of the corpus luteum. It is apparent by deductive reasoning as well as by interpretation of the facts described here that actual degeneration must begin, therefore, before the tenth or eleventh day of life of the corpus luteum. The studies on the urinary excretion of sodium pregnanediol glucuronidate by Venning and Browne (1937), Wilson, Randall, and Osterberg (1939), and Müller (1940) substantiate this. Definite regressive changes appear at approximately the

eighth to the tenth day. This time coincides with the termination of the so-called vascularization stage, or as suggested here, the termination of the period of essential function of the corpus luteum. These regressive changes are:

1. A marked decrease in the amount of blood in the vessels of the granulosa lutein layer and regressive changes in the vascular system.
2. Fatty degeneration and degeneration by simple atrophy of the granulosa lutein cells.
3. Increase in the amount of visible lipids in the granulosa lutein cells.
4. A sharp increase in cholesterol esters and a gradual diminution of the phospholipid content, as determined chemically.
5. Regressive changes in the endometrium.
6. A decrease in the amount of pregnanediol excreted in the urine, as determined by other workers.

Thus, since the peak of function is past, since the essential function is terminated, and since definite degeneration has set in, it is concluded that regression of the corpus luteum of menstruation sets in at the termination of the vascularization stage at approximately the eighth day of its life.

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DISCUSSION

DR. ROBERT MEYER, Minneapolis, Minn.—Dr. Brewer took exception to the idea of the stage of maturity or "bloom." These terms I used for the stage in which the connective tissue *begins* to cover the innermost layer of lutein cells. In the same way I applied the term "stage of proliferation" to the *beginning* of the striking multilayering of the granulosa cells after the rupture of the follicle, although the proliferation is already evident before rupture, and also, though to a lesser degree, later during the vascularization. Since the proliferation stage is short, one finds it only in follicles and not in the yellow body.

The term "maturity stage" I introduced in connection with two histological processes. In the beginning of the stage, which I called the stage of vascularization, the capillaries invade the proliferated granulosa, for the high point of internal secretion can only be obtained after the production of an arteriovenous network. The delivery of hormone into the blood is aided by the covering of the inner layer

of the lutein cells, because this hinders to a certain degree the secretion as well as the bleeding into the cavity. One finds fine lipoid granules in the granulosa cells, but these disappear more and more as the cells get larger and the nuclei appear vesicular. Since the same process goes on in pregnancy, my conclusion seems justified that these signs mean high degree of function. The findings of Chydenius of the finer cell structure (1926) supported my conception.

My first conception (1913), that the maturity or "bloom" extended from the seventeenth day until one or two days before menstruation, I modified later on, because I found the lutein cells in the inner layers already in regression by the twenty-second to twenty-six days. The term function I used always in connection with the behavior of the endometrium, but as menstruation I considered not only the bleeding but also the preparatory stage.

I agree with Dr. Brewer that we should answer the question of the nature of function principally from the point of view of fertility in general and of the nidation especially. I quote what I said in 1913, that "the culmination of the premenstrual development of the endometrium is not the stage of preparation for the nidation of the ovum. Preparation for nidation rather should occur at about the middle point between two menstruations, i.e., at the beginning of the premenstrual swelling of the mucosa. The culmination of the premenstrual phase would therefore be only the introduction to menstruation.

We first found the histologic evidence of regression of the corpus luteum on the twenty-second to twenty-fourth days of the normal cycle, as shown by vacuolization of the cytoplasm by large fat droplets in the inner rows of the lutein layer. Later evidences of regression during menstruation (softening of the fibrils, obstruction of the vessels, shrinking and sclerosis of the fibrils) appear first centrally and progress to the periphery.

The third of Dr. Brewer's points, namely the chemical analysis of the corpus luteum, is of special interest because for many years we endeavored to clear up the quantitative differences between the histochemically demonstrable lipoids and the real chemical content. We consulted authorities for the best methods and cooperated with highly trained chemists. The total content of cholesterol during the cycle is at first low, then it increases until "bloom" and until menstruation. The increase is due to the free cholesterol and not the cholesterol ester. During pregnancy the total cholesterol content is less, and it decreases more and more toward the end of pregnancy. The fatty acid changes considerably from case to case, but not in the various stages or in high degrees of regression. Lecithin increases until the histologic "bloom" occurs and decreases strikingly after menstruation, but in pregnancy the lecithin content is high and becomes very high near the end of pregnancy. The total amount of the lipoids does not differ essentially in the various stages of the cycle. More striking is the microchemically visible amount which is known to be high only during the time of regression. It is recognizable as big droplets at first found locally in single cells of the innermost layers. This progresses to the peripheral layers and after the menstruation involves the whole corpus luteum.

Stained lipoids are stored as very small particles before they accumulate in the cytoplasm. The invisible lipids are used for hormonal function. Large droplets mean regression.

To prove an early regression of the corpus luteum as a physiologic process, one must exclude damage, especially such as pressure by a myoma, and one must examine the basal part of the corpus luteum, because the superficial part is very often damaged. This may occur at any time of the cycle in large areas in the superficially prominent or capsular parts and it may be compared to the regression in the capsular part of an implanted ovum. Cystic corpora lutea and those with hemorrhage are also often damaged and therefore useless for study of normal physiology. The beginning of the regression does not mean cessation of the func-

tion of the whole corpus luteum, the outer layers of which may be well preserved for a much longer time.

The histologic appearance of the endometrium is occasionally not an absolutely reliable indicator of the functional potency of the corpus luteum and vice versa. In some cases described by Bartelmez and also in some demonstrated by myself, the corpus luteum histologically showed no regression some days after menstruation which occurred at the expected time. On the contrary, in other cases Bartelmez found the regression of corpus luteum without menstruation. This means that some unknown factors are interposed between the two organs, corpus luteum and endometrium, such as nerve controls or the internal secretion of other organs.

I believe it is of the greatest importance to stress the fact that the goal of all these processes is naturally pregnancy, and that menstruation is the sign of failure. Great difficulty is presented by the constitutional variations in individuals, which cause obvious differences of interpretation. Perhaps no other physiologic conditions are less balanced and stabilized. They are relatively recent acquisitions in phylogeny. The hormonal accord of the sexual procedures fluctuates between the physiologic and the pathologic.

DR. GEORGE VAN S. SMITH, BROOKLINE, MASS.—Mrs. Smith and I have found that luteal activity is reflected by characteristic changes in the amounts and partition of the urinary estrogens. These changes, corroborating Dr. Brewer's conclusions, point to maximum secretion of progestin between the fifteen and twenty-first days of a twenty-eight-day cycle with a peak between the nineteenth and twenty-first days.

What makes the corpus luteum wax and wane? From our studies of the relation between progesterone and estrogen metabolism we have formulated a plausible explanation. Progesterone reduces the rate of estrogen destruction in the body. Experimentally, estrogens may be so administered as to enhance and prolong luteal activity through stimulating the secretion of a pituitary luteinizer. Both in the menstrual cycle and in pregnancy the available evidence indicates that increases of estrogen secretion precede and accompany increases of progestin. We have come upon a factor in the urine of women which has a pituitary-stimulating effect similar to the estrogens and have concluded that it is formed as a result of estrogen breakdown and that it, rather than estrogens per se, is responsible for the observed luteal response to administered estrogens. It is not a pituitary substance, being heat stabile and ineffective in hypophysectomized rats. It is nonestrogenic but is found in the urine at the times when our studies indicate rapid destruction of estrogen, for example, during menstruation and the follicular phase of normal cycles and after the injection of estrogen in surgical castrates. In summary, we are well along on a trail of evidence to show that whenever estrogen is being rapidly destroyed a substance is formed which stimulates pituitary luteinizing activity and thus corpus luteum function and that, by reducing the rate of estrogen degradation, the corpus luteum prevents the production of this substance which is necessary for its survival.

We would explain the ovarian cycle, therefore, as follows: At the start of menstruation there is a sudden marked increase in the rate of estrogen degradation accountable to estrogen production in the absence of progestin. This sudden metabolic shift, which continues into the follicular phase, supplies the above-described factor as a result of which the pituitary secretes the luteinizing hormone, so necessary for ovulation and corpus luteum growth. Our studies indicate that by the twenty-first day of a twenty-eight-day cycle a minimal amount of estrogen is being destroyed due to maximum progestin secretion. The result is withdrawal of pituitary stimulation by the estrogen breakdown factor and consequent regression of the corpus luteum. The twenty-first day of a twenty-eight-day cycle would be the seventh to eighth day of life of the corpus luteum if ovulation occurs on the

fourteenth day. It is interesting that our time relationships, based on hormone changes as evidenced by urinary studies, should tally so closely with Dr. Brewer's, based on an entirely different type of investigation.

DR. JOHN ROCK, BROOKLINE, MASS.—In studying the corpora lutea from the seven normal previllous and villous human ova of 7.5 to 16.5 days of age, Miss Adams, our technician, and Dr. Hertig detected a decreased amount of neutral fat in the granulosa lutein cells when compared to the amount in the control nonpregnant corpora lutea of the twentieth to twenty-second day (sixth to eighth day according to Brewer's terminology) of the menstrual cycle.

In the nonpregnant, twentieth to twenty-second-day stages, they found a beginning nonfatty peripheral vacuolization of the granulosa lutein cells. With the onset of pregnancy this supposed evidence of active secretion was seen to increase and to remain a prominent feature throughout at least the first six weeks in the life of the corpus luteum.

Dr. Hertig has suggested therefore that the twenty-second day of the twenty-seven-day menstrual cycle (i.e., with catamenia on the twenty-eighth day), or the eighth day in the luteal phase of any cycle, is the critical point in the life of the corpus luteum. He believes that at this time implantation of the fertilized ovum, in some way not at present fully understood, but probably by its direct influence on the corpus luteum, causes the latter to continue and indeed to increase its secretory function, thereby postponing the degenerative and other changes which Dr. Brewer has covered in his paper.

DR. BREWER (closing).—It is an honor for one who is more or less beginning his work to have the privilege of having the primary author discuss his paper. It is to Dr. Meyer that we are all indebted for the essential work on the corpus luteum.

PARTIAL CONGENITAL APLASIA OF THE VAGINA*

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(From the Department of Gynecology, New York Post-Graduate Medical School and Hospital, Columbia University)

WITHIN the past twelve years, I have seen 12 cases of congenital absence of the vagina. Four of these were complete, 5 could be legitimately classified as a partial aplasia, and 3 were really developmental defects in pseudohermaphrodites. Three of the first 4 patients were subjected to the Frank-Geist "satchel-handle" operation with highly satisfactory results, all 3 being married; twelve years, five years, and one year, respectively. A colpoplastic operation was not suggested to the other patient since she was thirty-four years old, devoid of secondary female characteristics, and had no sex urge. Four of the 5 young women with a partial aplasia were operated upon and these constitute the subject of this presentation. The other was 27 years old, had been married three years, and had submitted to an inadequate plastic procedure elsewhere one year and a half previously with a poor result, but refused further surgical intervention. One of the three pseudohermaphrodites was operated upon against my better judgment because of her insistence, and this case is described briefly because it is the only instance in which I have transplanted the fetal membranes to line a newly created vaginal canal. The end result was surprisingly gratifying.

The patient was 22 years old and had never menstruated. At the age of four a general surgeon had opened the abdomen for the sole purpose of determining her sex. He reported to the parents that a vestigial uterus and two small ovaries were found high in the pelvis. At the age of twelve, after a two weeks' study at another hospital she was again pronounced a female. When this girl came under my observation in January, 1939, she insisted that an attempt be made to provide her with a vaginal canal because of her sex urge. Her urine contained 21.4 R. U. of estrin in a twenty-four-hour specimen and 16.1 R. U. per liter. Although there was scant anatomic evidence of female external genitalia and relatively little available space on the perineum between the lower margin of the urinary meatus and anus, the enlarged clitoris was almost completely amputated, and the space between the urethra, bladder, and rectum cautiously approached through a transverse perineal incision just above a miniature fourchette. The contemplated dissection seemed so hazardous that roentgenograms were taken with a catheter in the urethra and air distention of the rectum before the operation. This visualization of the field was of material aid in avoiding injury to the urethra, bladder, and rectum. After insinuating the exploring fingers between these structures up to the peritoneum, the

*Read at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

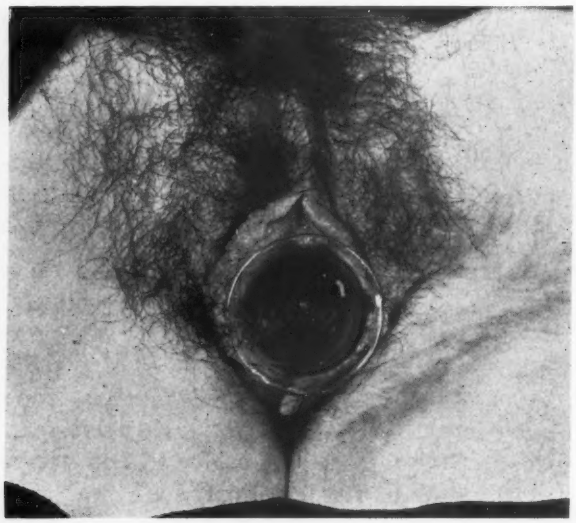

Fig. 1.—Typical end-result after the Frank-Geist "satchel handle" operation for congenital absence of the vagina. (Note slight scarring of area from which the skin flap was taken.)

Fig. 2.—End-result in a pseudohermaphrodite. Frank-Geist operation obviously impossible, because of profuse hair distribution. (Note developmental defect of normal labia.)

space thus developed was lined by implanting a generous section of fetal membrane, taken from another patient delivered by elective cesarean section within the previous hour, as suggested by Burger. (Membranes after rupture would obviously be useless because they would not be sterile.) The membrane was held in position with a glass phallus of appropriate size. Inspection at the end of two weeks disclosed small islands of epithelium throughout the canal as though pinch grafts had been transplanted. Although the cosmetic result is more picturesque than perfect, the artificial vagina appears functionally satisfactory (Fig. 2).

Many methods of establishing an artificial vaginal canal have been devised during the past century. They all include a transverse incision of the occluding membrane and separation of the cellular connective tissue between the bladder and rectum. Additional steps suggested, and their leading exponents are as follows:

Distending the canal with gauze packing, balsa wood, or Pyrex glass (Dupuytren, Kanter, Wharton, Meigs)

Implantation of isografts (Mackenrodt)

Transplantation of rectum (Sneiguireff, Popow, Menge, Schubert)

Transplantation of ileum (Baldwin)

Transplantation of flaps from the labia (Bumm, Puppel, Graves)

Transplantation of skin flaps from the thigh (Beck, Frank-Geist, Grad)

Implantation of fetal membranes (Burger)

Transplantation of Thiersch skin grafts (Kirschner-Wagner) and with mastic solution (Counsellor)

One of the originators of the Frank-Geist operation has reported five recent cases in which he secured a satisfactory canal, without an incision or operation, by forcing the mucous membrane of the obstructing partition inward by means of glass test tubes. The patient is taught to introduce a narrow tube into the hymenal ring with backward and inward pressure. After one week the direction of the pressure is changed to that of the normal vaginal axis, and as dilatation with indentation progresses, larger tubes are used until the new canal is adequate for coitus. This bloodless and simple method would seem the most desirable of all, but unfortunately proved entirely inadequate in the only two cases in which I have tried it, probably because of the unwillingness of the patients to subject themselves to so much controllable discomfort.

The four patients operated upon for partial aplasia of the vagina had certain features in common. They were all young, attractive girls, with a typical female body contour, well-developed breasts, and pronounced secondary sex characteristics. None had ever menstruated. The external genitals were well developed, and each had a rudimentary vagina about one i[illegible] in depth. The blind end of this tiny pouch was apparently a composite of occluding membrane and tough hymenal partition. True partial congenital aplasia should not be confused with a somewhat similar condition seen far more often, in which there is simply a developmental gynatresia of a vaginal canal of normal length with an abnor-

mally small introitus and an extremely rigid and sensitive hymen, which in some cases is situated from 1 to 3 cm. above its normal location. All four patients were treated in the same way, by making a transverse incision through the obstructing upper limit of mucous membrane, progressive finger dissection between the bladder and rectum up to the peritoneum, and inserting the largest size glass phallus which the newly created space would accommodate. The glass vaginal obturators I have used are shaped much like the anatomic phallus, except that they have a little indentation near the outer margin which precludes pressure on the overlying urethra (Fig. 3).

The first patient, single, aged 28 years, was operated upon in August, 1939, and has been happily married since March, 1940. She reports that coitus is normal in every way, but is still wearing her glass plug. The second patient was single, aged 18 years, was operated upon in February, 1940, and has worn the plug continuously ever since. The third patient, aged 23 years, was operated upon in March, 1941,

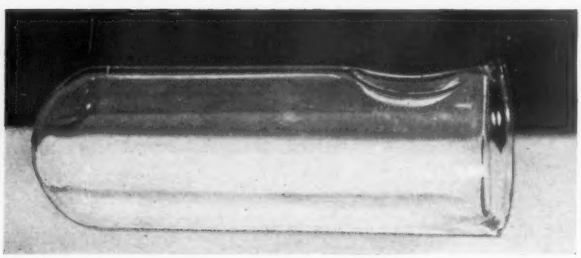

Fig. 3.—Glass tube used for maintaining vaginal dilatation. (Note indentation near outer margin to avoid pressure on overlying urethra.)

immediately after her husband had left her, because after four years of marriage, attempts at coitus had never been successful. Although hopeful that correction of the anatomic defect would enable her to reestablish her home, the husband failed to return. However, she was subsequently treated by another physician for an acute gonococcal vaginitis. She is a timid individual, who does not tolerate discomfort well and consequently failed to maintain enough pressure on the vaginal obturator, so that in October, 1941, it was necessary to again enlarge the upper end of the canal, which showed evidence of moderate contraction. In April, 1942, she developed an inguinal hernia and was operated upon in another city. The surgeon reports: "I found a tube and ovary which appeared normal, in the inguinal canal, separated the tube and ovary from the surrounding tissues of the canal, and replaced them in the abdominal cavity. On palpation through the internal ring with one finger, I thought I felt the fundus of a small uterus, but could not be sure. I did a regular Ferguson repair of the hernia." The fourth patient, aged 20 years, had been separated from her husband after four months of marriage and was operated upon in October, 1941. After wearing a large plug for three months, the husband returned and coitus has been normal ever since.

The outcome can be regarded as quite satisfactory in all four cases since the canals were well epithelized within three months; three of the patients are using their new canals physiologically, and the other one has adequate space for normal coitus. It is universally recognized that all artificial canals manifest a tendency to contraction if dilatation is not maintained for a long time. Hence, it is advisable to keep the patients under observation and to insist that they wear the glass phallus for many months if married and continuously if single. Faithful cooperation is important, for if the patient shrinks from a mild discomfort and fails to exert sufficient pressure on the vaginal obturator, contraction may occur. In the cases cited there can be no doubt that the squamous cell epithelium lining the upper part of the vaginal recess crept in from the margins of the lower vaginal area which had been incised and stretched. Burger contends that when a new canal is lined with fetal membranes, there is actual epithelial transformation, because epithelization takes place as early as six days after the membranes have been implanted, and this is too soon for extensive proliferation to occur. He believes that the amniotic epithelium possesses the same physiologic characteristics as the epidermis, both showing the presence of glycogen. Sections of fetal membranes were used as transplants by Burger's ophthalmologic colleagues at his suggestion in four cases of symblepharon, to replace the lost conjunctiva, with subsequent development of stratified epithelium.

In the earliest cases of congenital absence of the vagina reported in the literature, the operation consisted of simple dissection of the adventitious connective tissue between the bladder and rectum, followed by packing the newly created space with gauze. This procedure was described by Dupuytren as early as 1817, but he and others soon found that this method was followed by prompt contraction and epithelization. Wharton has reported excellent results in 65 per cent of cases after the introduction of a balsa wood obturator covered with two layers of condom rubber, and Meigs has used Pyrex glass plugs in the same way. Packing the canal with any soft and compressible material predisposes to failure because there is no resistance to rapid contraction which occurs before epithelization can progress to any great extent. Since the squamous cells must proliferate from the margins of the introitus, it seems logical to continue the use of some variety of skin transplant in cases of complete absence of the vagina, or to adopt Frank's suggestion to apply pressure with test tubes on the occluding membrane without incision, if the patient can be induced to apply and maintain sufficient pressure. In cases of partial aplasia, however, a serviceable canal can be prepared within two or three months by introducing a glass plug into the newly created space between the bladder and rectum, with little discomfort to the patient. Regardless of each individual operator's preference for a particular technique, it seems quite evident that the

elaborate and hazardous operations involving an intestinal resection can be completely discarded as unnecessary.

580 PARK AVENUE

DISCUSSION

DR. JOHN E. HOBBS, ST. LOUIS, MO. (By Invitation).—The operative procedures to create an artificial vagina are limited as far as I am concerned to two and possibly a third method. In all cases where there is an absence of the uterus or a hypoplastic uterus that does not function, I believe Frank's method of forcing the mucous membrane of the obstructing wall inward by means of a glass test tube should be attempted. The method is simple, not dangerous and nonconfining. If results are not satisfactory, one has not created any additional difficulty for any operative method desired. If Frank's method fails in these cases, or if a functioning uterus is present, it seems to me that the choice of operative procedure is the one selected by Dr. Dannreuther in the cases just described, that is a variation of the method championed by Wharton and Meigs. I wish to report briefly the two cases.

CASE 1.—M. P., aged 18 years, sought medical attention because she had not menstruated, and her local doctor told her she had an imperforate hymen. The physical examination revealed a normal girl with the exception of the lack of a vagina and uterus. She had hypertrophy of the clitoris and labia minora. There was a small dimple above the fourchette without a vaginal opening. A rectal examination revealed no evidence of hematocolpos. A small firm nodule 2 x 2.5 cm. was felt in the uterine region. A cordlike structure was palpated in both adnexal regions with what was considered to be normal gonads at either end. She was engaged to be married and wanted surgical intervention.

A transverse incision was made in the obstructing membrane and a tunnel was constructed between the bladder and rectum up to the nodule felt in the uterine area. A canal 4 inches deep and 2 fingers in breadth was formed. An obturator of dental wax was made and full thickness grafts from the inner aspects of the labia minora were cemented (epithelial surface only) to the obturator with rubber cement. The obturator with the grafts on it was inserted into the canal and maintained in position by placing an eye-screw in the outer end of the dental wax dilator. A small rubber tube was passed through the eye-screw, carried between the buttocks and thighs and each end of the tubing was attached to a band placed around the body above the ilia. The patient could wear the obturator with comfort, void with ease and without disturbing the dilator. She could have pitcher douches without ever any chance of the obturator being displaced. The dilator was removed on the 18th day and islands of epithelium appeared in the tract. Rapidly the tract became epithelized.

In about three months after the operation she married, and her sexual life has been normal for about three years. I received a letter from her a few days ago, stating she is happily married and enjoys coitus.

CASE 2.—M. G., aged 16 years. At 12 years of age this patient started having severe cramps and fainting every month but never any flow. In May, 1941, her local doctor incised what he thought was an imperforate hymen and found there was a total lack of a vagina. He made a small tunnel between the bladder and rectum, and after reaching what he thought was a cervix, a considerable amount of old blood came out. He placed a gauze pack in the canal but it gradually became constricted. She had two periods of scant flow after this procedure. At the time I saw her, two and one-half months later, she appeared to be a normal girl, well developed and in good health. On examination of the genitals the labia minora were hypertrophied, and the clitoris normal. The canal was completely

closed, and only a dimple existed above a well-formed fourchette. A transverse incision was made, and again the rectum and vagina were separated by both blunt and sharp dissection. There was considerable scar tissue which had to be freed by sharp dissection. At a distance of 3½ inches a tight constriction was reached which was dilated with great difficulty. I could not convince myself that this was a cervix. A uterine sound was passed beyond the constriction to a depth of 2½ inches, which I believed was the upper limit of the vagina. I could never get the constriction dilated enough to expose a cervix above. Two full thickness grafts, about 2 x 3 cm., were removed from the inner aspects of the labia minora and tied with fine catgut about a large test tube, 1½ inches in diameter. The tube was held in position by placing a rubber stopper in the tube and an eye screw in the rubber stopper. A small rubber tube was placed through the eye screw and secured as described in the other case. The test tube was removed the first time in one week. At that time the canal was 5 inches long and admitted 2 fingers. I could not be certain whether or not the grafts were growing. There was great difficulty in keeping the upper portion of the canal dilated. Finally a biopsy was taken and the constricted portion contained cervical glands. Normal endometrium was obtained from higher up. Therefore, the constricted portion was cervix, which was and still is flush with the vaginal walls. The vagina then measured about 3½ inches. The canal is completely epithelized and has now been lengthened to about 4½ inches by pressure of the tube worn at night. The patient menstruates regularly and without pain.

My observation of these two cases convinces me that any type of graft is unnecessary. The vestibular epithelium will grow in and line the tract satisfactorily.

The third method of implantation of fetal membranes, as proposed by Burger and used in one case by Dr. Dannreuther, is most intriguing. However, I have always been skeptical about the growth and persistence of this tissue. Brown and McDowell have shown that homotransplants of skin that appear to grow early always disintegrate in three to six weeks, and then the epithelium grows in from the edges at a rapid rate, giving the ordinary observer the idea that the graft has persisted. It is Brown's opinion that no homotransplants persists, even homotransplants of cartilage become fibrotic months afterward. If the entire tract can become lined in four to six weeks without any epithelial transplants, it seems difficult for one to evaluate with any certainty the value of transplants. However, if it were established that fetal membranes do not grow or persist it seems to me the membrane might serve as a dressing to the raw surfaces and perhaps serve as a guide for the ingrowing epithelium. In collaboration with Brown and McDowell, I have some investigative work in progress in an attempt to determine the growth and viability of fetal membranes when transplanted.

DR. NATHAN P. SEARS, SYRACUSE, N. Y.—I have seen 8 cases which might well be discussed at this time. Six of the patients had complete absence of the vagina; one had a partial aplasia, and the other appeared to be a true hermaphrodite.

The six cases of complete aplasia were treated in the following manner:

CASE 1.—A well developed, normal girl of 19 years with female characteristics had never menstruated. Without a pelvic examination she was given considerable ovarian hormone by a general practitioner which, of course, produced no effect. This girl was subjected to the Frank-Geist "satchel-handle" operation and has a vagina about 3½ inches deep but lined with coarse skin bearing many hairs and secreting much sebaceous material. Unfortunately, her plans for marriage have not materialized.

CASE 2.—A woman of 22 years was engaged to be married and had had one unsuccessful operation in another city. When seen by me she had a very small

tortuous sinus leading from the perineum for several centimeters between the bladder and rectum. The Frank-Geist operation was done, the greatest difficult being to create a cavity to which a tube graft could be applied as the scar from her former operation was extremely difficult to handle. A good graft was finally established but, much to my disgust, on removing the plug the entire graft came out. I then had her wear a ⅞-inch test tube in the vagina constantly for four weeks and after that for a varying period of one-half to two or three hours a day. She has been married for several years, has perfect marital relationship and has a very pliable normal vagina.

CASE 3.—The third patient, 21 years of age had been married six months, but complained that intercourse had not been completely satisfactory. On examination she was found to have a definite pouch 2 inches deep between the rectum and bladder. On closer questioning I found that she had been attempting intercourse since she was 14 years old, which led me to conclude that the pouch had been produced by attempted intercourse over a long period of time. This patient consulted me only once and I do not know whether or not she has improved as time went on. I advised against any surgery.

CASE 4.—This case came to the clinic after one attempt had been made at another hospital with complete failure. This girl was mentally deficient and the Department of Charities and Social Workers were very much against having any more work done. With this plan I heartily agreed.

CASE 5.—This woman of 26 had never menstruated, but came with the statement that she was to be married in eight weeks. She was instructed in the use of Dr. Frank's method of gradual invagination by graded test tubes and she had a perfectly normal 3½ to 4 inch vagina at the end of seven weeks. When seen after her marriage she stated that her marital relationship was perfectly satisfactory.

CASE 6.—The next patient of the group was 50 years old and had been married 30 years. At the time I saw her she had two large pelvic tumors and the surgeon called me because he was unable to feel the cervix properly. A large mass was present in the right side of the pelvis which seemed to be a fibroid and another mass in the left inguinal canal extending to the labia. When I examined her, I found that she had no vagina but had created a deep pouch during her thirty years' marriage. When her abdomen was opened, it was found that she had a double uterus, each containing fibroids, the left uterus being incarcerated in the left inguinal canal. The two halves of the uterus were removed and no lumina were found.

CASE 7.—The next case was one of partial aplasia. This patient did not know there was anything wrong until after her marriage when she presented herself to her physician, pregnant. A diaphragm with only a small opening was discovered in the upper third of the vagina. By cesarean section she had two children. When I saw her she was rather nervous and apprehensive and complained of very unsatisfactory marital relationship. Two or three attempts had been made to establish a normal vaginal canal with rather poor success. The diaphragm was cut away and a glass plug was inserted and kept in place constantly for four weeks and then used about twice a day for about six weeks. The raw surface left by the incision of the diaphragm covered over nicely with epithelium and she now has a normal vagina with the cervix easily visible although somewhat shortened.

CASE 8.—The last case was one of true hermaphroditism. This girl of 11 had just started to menstruate but the blood apparently came through the urethra. Examination showed a normal appearing girl with developing breasts and normal pubic hair. In the left inguinal canal was a firm, tender mass the size of a small

lime which seemed like a hernia but could not be reduced. She was advised to enter the hospital for study but before her hospitalization was effected the mass in the right groin became very painful and surgery seemed an immediate necessity. Incision of the inguinal canal revealed a black organ which looked like an ovary. This was removed and a hernial repair done. Sections of material removed, although somewhat distorted, resembled testicular tissue, and no evidence of ovarian structure was seen. She made an uneventful recovery but so far I have not been able to follow up her case to determine the complete picture of this congenital anomaly.

From my experience with these cases it seems evident that the more formidable operations can now be discarded. Case 2 indicates that practically no graft is necessary when the open operation is done. This corresponds very well with the experience of Meigs, Wharton and others, namely that if the canal is kept open with a nonirritating glass plug, epithelization will take place. I agree with Dr. Hobbs that we have no evidence to prove that the tissue put in these patients is actually the source of the epithelium which lines the canal. However, from my experience with the 3 patients who either by themselves or by test tubes produced vaginal canals by pressure, it seems this method is the simplest and will probably be the most universally used.

In closing I wish to say that I think any young woman so unfortunate as to be born without a vagina when she has the hope for marriage should have a vagina created.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—I should like to report a successful case treated by the bloodless tube method. When the patient was 13 years old she had not menstruated and was having a great deal of periodic abdominal pain. Her doctor, thinking she had an imperforate hymen, made an incision, obtained nothing, and desisted from further attempts. She continued to have these periodic attacks of pain which ultimately became continuous. This was the stage at which I saw her.

On rectoabdominal examination one could make out a tense swelling to the left side of the pelvis and a tentative diagnosis of occluded double uterus was made. She had no vagina. It was found at operation that one horn was distended and occluded, the other quite small; both tubes and ovaries were perfectly normal. Both horns were removed and nothing more done. The girl was not told anything about the absence of the vagina at that time. When she was nearly 19 years old, she became interested in a young man and was determined that she was going to marry him. She had normal sexual reactions and normal secondary development. We began treatment by the Frank method. There was a small depression where the first incision had been made. She used larger and larger dilators and was very conscientious in their use. About ten months after the treatment was begun she was married and has now been married for about one year. The marriage is perfectly happy and successful.

DR. ROBERT MEYER, MINNEAPOLIS, MINN.—In a critical review of the literature of hematocolpos, hematometra and hematosalpinx (1895) I pointed out that the occlusion in most cases was acquired by inflammatory processes presumably caused by infectious diseases of childhood.

The use of the term "aplasia of the vagina" means that it was never formed or strictly that it is a developmental anomaly. This can be caused by a primary defect of the lower end of the Müllerian ducts, either total or partial. The Müllerian epithelium can undergo regression soon after its early appearance in females as well as in intersexes, which is of course also the fate of the Müllerian ducts in most of their extent in males.

The vagina takes its origin from the Müllerian ducts only topographically, and not histologically. The Müllerian epithelium, after having built the vaginal canal, undergoes full regression and is replaced by the sinus epithelium which is of an entodermal nature. I can show you this in only a superficial way in a few photographs selected from more than 3,000.

I cannot omit mentioning that the hymen is formed by foldings of the vestibulum, the former entodermal sinus urogenitalis. An "imperforate hymen" cannot exist because it is open from the beginning. An occlusion must be the result of the growing together of the foldings at their margins. As a rule the so-called imperforate hymen is confused with a membrane-like atresia of the vaginal introitus.

When the Müllerian epithelium has not yet made contact with the sinus, the epithelium of the Müllerian vagina ripens to mucous epithelium as it does in the cervical canal. In fact in malformations, which one finds in newborn children and in cases of hematocolpos in the adults, the open or canalized part of the vagina is covered by mucous epithelium, as I found in some cases. If an excision of the occluding membrane is made, mucous epithelium will be found on the upper side as proof that the atresia is congenital.

Some locally persistent portions of Müllerian epithelium in the otherwise squamous epithelium-lined open vagina give rise to cysts, glands, and eventually adenomas and adenocarcinomas as in the cervix. In every case of congenital partial atresia of the vagina one should examine the mucosa to obtain information to aid in determining whether or not the Müllerian epithelium can change into squamous epithelium. Certainly one must be sure that in a double vagina if unilaterally occluded, the closed side does not communicate with the other normally developed side even through an opening in a cervical septum.

Finally I should like to raise the question of how the Müllerian epithelium in the vagina changes after the removal of the occluding membrane. One may ask not only if it becomes a squamous epithelium histologically but also how does it behave functionally? What is the content of glycogen; are there Doederlein bacilli; and are there cyclical changes? Do intestinal transplants act in the same or a similar way?

DR. NORMAN F. MILLER, ANN ARBOR, MICH.—I would like to raise a question in connection with this very interesting subject. It has been stated from time to time that "split thickness grafts" used in the reconstruction of artificial vaginas probably die and are replaced by epithelium from the vestibule or vulva. I am inclined to agree that this may occur but the point has not been proved.

We have been much interested in just what happened to the split thickness grafts and recently had occasion to study a patient in whom we had obtained a healthy take. The patient had complete absence of the vagina but did have tubes, uterus, and ovaries. At the time of admission she presented a hematometra and bilateral hematosalpinx. A channel was made and the accumulated blood drained off. Ten days later a split thickness skin graft was applied on an obturator which resulted in an excellent take. Three months later we studied this girl carefully and biopsies taken from the new vagina demonstrated typical vaginal epithelium. Whether this was a conversion of the transplanted epthelium into the vaginal type because of its new environment or whether the graft tissue had been replaced from the vestibule is something that further studies will have to determine.

DR. EMIL NOVAK, BALTIMORE, MD.—Like the previous speakers, I believe that the days of the more formidable procedures, such as the Baldwin operation, in the construction of an artificial vagina have passed. In former years I performed a number of these operations, and I still feel that the anatomic and functional results obtainable by this method surpass those following the employment

of the simpler and safer methods now in vogue. At the meeting of the American Association of Obstetricians and Gynecologists in Baltimore two years ago I showed the end results in one or two of these patients a good many years after operation, and I believe that those members who examined the patients agreed that the artificial canal could scarcely be distinguished from a normal vagina. However, in view of the magnitude of this operation and the inevitable element of risk, it has very properly been superseded by simpler methods which give very satisfactory if not always ideal results.

The particular point which I rose to discuss has already been touched upon by Dr. Meyer, to whom we are all indebted for his monumental researches in the embryology of the vagina. In certain cases of pseudohermaphroditism the vagina appears to be completely absent, while the urethra occupies essentially its normal position, often connected by a shallow furrow with the clitoris. By means of endoscopic studies and cystograms, however, the vaginal canal, often rather small and rudimentary, will be found to enter the urethra at an acute angle a short distance behind the meatus. In such cases it is possible by a very simple plastic procedure to open the vagina to the exterior, and the mistake of unnecessarily creating an artificial canal in the perineal body thus avoided. I have encountered two such cases in the past few years. The anomaly in these cases is an absence of the septum which subdivides the lower urogenital canal into an urethral and vaginal portion. It is easy to understand, therefore, that in such cases menstrual bleeding may occur from the urethra, and I believe that one of the cases reported by Dr. Sears will probably fall into this category.

DR. JOSEPH L. BAER, CHICAGO, ILL.—I have a report from a totally different category of a girl of 16, one of uniovular twins, the other being entirely normal. The patient presented herself with a pelvic mass of very considerable size, aplasia of the vagina and only a slight dimpling on the perineal surface. Through a transverse incision I tunneled down until what seemed to be the cervix was exposed. By probing I found the cervical canal and evacuated the huge retained menstruum.

Because of this patient's youth I had no desire to do an extensive tubular transplant, nor to begin the routine of glass tubes to maintain a vagina. Instead I anchored the cervix as close to the margins of the perineum as I could by heavy traction sutures, producing an artificial prolapse, if you please. This healed entirely, and five years after the operation she returned happily married. The vagina had constructed itself. Evidently the prolapsed uterus withdrew, the vulvar margin came up with it and she had an 8 cm. vagina.

DR. DANNREUTHER (closing).—I would like to make three points in commenting on the previous discussion. First, the results are much better, no matter what type of operation is done, if the surgical procedure is deferred until the patient plans to use the canal physiologically. Second, the hair on the inner aspect of the thigh seems to be a handicap in some candidates for the Frank-Geist operation, but I have overcome that by referring my patients to a dermatologist for removal of the hair by electrolysis. Third, it is easy to make frequent observations through the glass obturator and thus follow the process of epithelization in the new vaginal canal.

A BACTERIOLOGIC STUDY OF PYOMETRA*

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PYOMETRA is defined as an accumulation of pus within the uterus. The earliest recorded report of pyometra which we could find was "Case of a collection of pus in the cavity of an unimpregnated uterus," by J. Clarke[1] in 1812. This report was found in the first series of the index catalogue of the Library of the Surgeon's General Office. In this same series were found reports of either a collection of pus in the uterus, or a discharge of pus from the lining membrane of the uterus, by D. Schutte[2] in 1828, by Ashwell[3] in 1837, by Hyndman and Storer[4] in 1853, and by Taliaferro[5] in 1873. Undoubtedly there are earlier reports in the foreign and American literature.

Sporadic case reports of pyometra appeared in the literature of the late eighteen hundreds and in the early nineteen hundreds. There was a paucity of reports in the American literature.

In 1912, Loman[6] reviewed the literature and quoted the incidence of pyometra given by Sainclair, Berkle, Lewers, Tate, Lee and Bazy. He also discussed the causes, symptoms, classification, and pathology. His report was based on a study of patients with carcinoma of the cervix.

A review of the literature shows that pyometra was found commonly before radiation therapy was used clinically. After the advent of radiation therapy most case reports were of pyometra following the treatment of uterine cancer with radium and x-ray.

In 1915, Roberts[7] reported a patient in the postmenopausal age who had pyometra without carcinoma of the cervix or uterine corpus. In 1923, Lammers[8] reported pyometra in a patient treated by radium and x-ray for carcinoma of the cervix, and in that same year Alamanni[9] reported three patients with carcinoma of the cervix, for which no radiation or operative therapy was used, in whom pyometra developed. In 1924, Condamin[10] reported pyometra in a patient with carcinoma of the cervix treated with radium and x-ray. In 1927, Violet[11] found pyometra at hysterectomy in a woman of 65 years with carcinoma of the corpus of the uterus. In 1927, Esser[12] reported an operation upon a woman of 60 years with carcinoma of the vagina, cervix, and uterus; 2,000 c.c. of pus were found in the vagina, cervix, and uterus. In 1928, Reeb[13] reported the finding of a calcified concretion, or uterine stone, blocking the cervix with resultant pyometra in a woman of 77 who had had at the age of 44 a dilatation and curettage and radium therapy for a small fibroid of the uterus. In the same year Guyot, Jeanneney, and Varrin[14] described pyometra and hematometra in a patient with carcinoma of the cervix, before and after radiation ther-

*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

apy. Stacy,[15] in 1928, in discussing the complications of radium therapy to pelvic lesions, did not report pyometra specifically but mentioned it in his discussion. In 1929, Godleweski[16] reported pyometra in a woman of 30 years who was operated upon for a twisted, infected dermoid cyst and who, one year previously, had had acute gonorrheal cervicitis and salpingo-oophoritis for which she had received vaccine therapy. Pride[17] in that same year gave a report of a patient of 28 with a submucous fibroid, but with no cervical stenosis, in whose uterine wall was found an abscess containing 500 c.c. of pus.

In 1929, Bland[18] reported pyometra in three patients who previously had received radium therapy for uterine cancer. His article reviewed the etiology, classification, symptoms, prognosis, and treatment in pyometra. Middleton,[19] in 1931, published his report of pyometra in a pseudohermaphrodite. The pyometra was first drained and later the uterus was removed. Remmelts[20] in the same year reported pyometra in a woman of 43 years with carcinoma of the cervix who had received no radium or x-ray therapy. In 1932, Guilhem and Gouzy[21] reviewed the subject of pyometra in carcinoma of the cervix after radium therapy and discussed the predisposing causes, the pathology, the clinical forms, and the preventive and the curative treatment. They emphasized the fact that infection was present in all cervices with carcinoma and stated that the streptococcus was always present, but was rarely hemolytic, and, therefore was less virulent. Liegner,[22] in 1930, described a diabetic, aged 57 years, who had a small submucous fibroid and stricture of the vagina with retention of pus in the vagina and uterus. She had no cancer. Barrows,[23] in 1934, listed pyometra of the cervical stump in a patient who previously had had performed bilateral salpingo-oophorectomy and supravaginal hysterectomy. In 1934, Hirsch[24] reported pyometra in a patient who had adenocarcinoma of the corpus of the uterus and who eight years previously had received radium therapy for carcinoma of the cervix. Gemmill,[25] in 1934, reported pyometra, with 600 c.c. of pus in the uterus, in a patient who was pregnant three or four months.

Massbuau and his group[26] in 1935 reported a woman of 64 years, who had received radium therapy five years previously for carcinoma of the cervix, and who developed carcinoma of the corpus of the uterus with pyometra. In 1936, Szathmary[27] found pyometra in the uterus of a woman of 63 years who also had granulosal cell tumor of the ovary.

Weinstein, Gardner, and Allen,[28] in 1937, attempted to show that the injection of estrogenic substance in mice tended to produce pyometra. Bacteria were present in higher percentages in the uteri of the mice which received the hormone than in the uteri of a control group of mice. In 1938, Grenier[29] reported pyometra in five patients after radium therapy for carcinoma of the cervix. Carriere, Gineseste, and Devos,[30] in 1938, reported a patient of 64 years who had no carcinoma but who developed peritonitis from spontaneous rupture of a pyometra. Smears from the pus showed mixed organisms but full bacteriologic studies were not done.

In 1939, Loranger[31] reported a patient of 22 years with a sterile pyometra who previously had received numerous injections of estrogenic substance. He quoted the experimental use of estrogens to produce pyometra in mice and theorized that estrogenic substance might produce pyometra. Graham and Failla,[32] in 1940, found a spontaneous occlusive pyometra in a woman of 73 years who had no carcinoma.

Smears from the pus were positive for gram-negative intracellular diplococci and mixed organisms. Cultures were reported positive for mixed organisms, but it was not stated that the gonococcus was found.

PATHOLOGY

Certain predisposing pathologic conditions antedate the formation of true pyometra. Loman[6] stated that normally the uterine secretion was small in amount and free of bacteria and that the physiologic function of the cervical secretions and coverings was the destruction of bacteria. In cancer of the cervix the resultant circulatory disturbances favored infection. He quoted Bazy who claimed that cancer of the cervix was limited to the lower part of the cervical canal. The mucous membrane of the canal above the cancer growth was ulcerated and covered with pus. Swelling, due to capillary and lymphatic dilatation, occurred. Bazy considered this process one of inflammation of the cervical canal with sclerosis and lymphangitis. Loman gave as causes of pyometra new growths which constricted the cervix, atresia due to the sclerotic atrophy which occurred after menopause, and a cancerous swelling which acted as a valve by forcing itself into the cervical canal.

Bland[18] listed as possible causes of pyometra any condition which causes partial or complete obstruction of the cervical canal, inflammatory edema about the cervical os, senile fibrosis, endometrial vegetations and polyps, myomas, chemical ulceration followed by fibrosis, malpositions of the uterine body and congenital gynatresia. His article stressed postirradiation pyometra and emphasized the fact that radium converted neoplastic tissue to dense fibrous tissue which in turn contracted and caused fusion of the walls of the cervix. The fluid accumulation in the uterine cavity resulted from associated inflammatory changes in the endometrium and the myometrium, lesions almost invariable accompaniments of cervical carcinoma. That the fluid accumulation was inflammatory in origin was predicated upon the observation that the normal secretion of the endometrium was practically nil. Since the cancer tissue contained all forms of pathogenic bacteria, the fluid in the uterine cavity was readily infected.

Guilhem and Gouzy[21] discussed pyometra after radium therapy in cancer of the cervix and gave as a predisposing cause the inability of the uterine secretions to escape through the os. Radium therapy modified the distribution of the tubular glands in the mucous membrane of the uterus and insufficient radium dosage and incorrect intracervical application caused some glands to be destroyed whereas other glands continue to secrete. They also claimed that infection of cervical cancer always occurred and that streptococci were always found in the cancer tissue. The streptococci found were rarely hemolytic and as a result were less virulent. Since bacteria were present before, during, and after treatment, increased uterine secretion resulted not only from the presence of infection but also from the tissue destruction which radium caused. This tissue destruction itself caused increased secretions. Other pathologic lesions of the cervix caused uterine secretions to be retained. Due to the degeneration of the muscular wall of the uterus following radiation therapy with the loss of uterine contractility, and to the cervical stenosis, distention of the uterine cavity occurred. The true determining causes of pyometra were due to the radiation sclerosis of the cervix with partial or complete stenosis. In postirradia-

tion pyometra they described the anatomic pathology as follows: the cervix reduced to a stump with the vaginal portion deformed or destroyed; the uterine wall thickened; the uterine mucosa purple or grayish in color; the endometrium the site of the endometritis; interstitial metritis later with ulceration; inflammation around the uterus with adnexal lesions and adhesions; varying quantities of pus of different colors in the uterine cavity.

BACTERIOLOGY

The importance of infection, in the predisposing pathologic conditions antedating the formation of pyometra, was stressed in the foregoing reviews of the pathology. No studies of the bacteriologic findings in pyometra could be found since anaerobic cultural methods have been proved to be of fundamental importance in the study of pelvic infections. The routine use of these culture methods has changed our concept of pelvic infection so markedly that it seemed logical to study the bacteriology of pyometra by complete anaerobic and aerobic cultures.

Bacteriologic studies in our clinic of the cavities of large myomatous uteri removed in the childbearing age and of the cavities of small senile uteri removed by vaginal hysterectomy in descensus and procidentia had shown that the cavities in these uteri were sterile if rigid technique were used in the method of culture.

MATERIAL

Complete aerobic and anaerobic cultures of the pus from 39 patients with pyometra were done. Aerobic cultures were done of the pus from 6 patients with pyometra, and no cultures were obtained from 3 patients. The high incidence of anaerobic organisms in pelvic infection made incomplete the studies in which only aerobic cultures were done.

Collection of Material.—In the collection of the pus for culture, the possibility of vaginal and cervical contamination could not be entirely excluded. Routine precautions prior to culture to prevent contamination included the washing of the vagina and cervix with green soap and alcohol. This preparation of the vagina and cervix was used prior to the sounding of the cervices and uteri of all senile patients, of all patients who had operations upon the cervix and of all patients who had been or were to be treated by irradiation therapy. When sounding of the cervix was indicated in the childbearing age due attention was given to the menstrual history of the patient, and in many patients, pregnancy tests were done prior to the sounding of the cervix and uterus.

After the cervix had been dilated by a sound, or by a probe, a very small metal cannula was passed into the uterine cavity. In most patients the amount of pus present in the cavity was sufficient to make possible cultures without obvious contamination.

An important check on the method of collection was a routine examination of smears, prior to culture. In a majority of the patients the results of cultures confirmed the findings of the smears made of the pus.

Culture Methods.—For the growth of aerobic organisms the pus was streaked directly on beef infusions, sheep's blood agar plates. For anaerobic plate culture the same medium was used, but the plates were placed in anaerobic jars and a slight modification of the hydrogen replacement method, as described by McIntosh and Fildes,[33] was used.

TABLE I. PYOMETRA COMPLICATING SQUAMOUS CELL CARCINOMA OF THE CERVIX (NO PREVIOUS RADIATION OR OPERATIONS) (12 CASES)

HIST. NO. RACE—AGE PARITY	CLINICAL SYMPTOMS				ASSOCIATED DISEASES	OPERATIVE FINDINGS (C.C. PUS)	BACTERIOLOGIC FINDINGS	FOLLOW UP
	VAGINAL BLEEDING AND DISCHARGE	PAIN	FEVER	LEUCOCYTOSIS				
86155 W—54 yr. 11-0-9	+	−	−	−	Carcinoma, nose	1500	No growth	Living
79772 W—69 yr. 12-0-1	+	+	−	−	Senile vag. dysuria	40	No growth (aerobic only)	Living
64878 W—52 yr. 16-2-12	+	+	+	+	Pyelitis—Cystitis; R.V.O., small cystorectocele	10	Not done	0
66739 C—44 yr. 13-1-9	+	−	+	+	Redundant vagina, dysuria	300	Strep. viridans (aerobic only)	0
58905 W—50 yr. 13-0-1	+	+	−	−	Vaginitis	10	Staph. aureus (aerobic only)	0
91771 W—52 yr. 2-0-2	+	+	−	−	Stricture of ureter	30	No growth	Living

A16883 W—56 yr. 8-1-7	+	−	+	−	Obesity	20	Anaerobic strep. strep. gamma	Living
97246 W—80 yr. 5-0-4	+	+	−	−	—	10	Diph. bacillus	0
A55853 W—53 yr. 4-0-4	+	−	+	+	Lac. perineum constriction upper vagina	150	Mixed anaerobes	0
A42183 W—65 yr. 9-0-5	+	+	+	−	Senile vaginal and vulval changes	200	Mixed anaerobes	0
A63108 W—69 yr. 8-1-7	+	−	−	−	Atrophic changes genitalia	75	Anaerobic cocci	Living
A48530 W—56 yr. 0-0-0	+	+	−	−	Obesity	100	Staph. aureus	Living
Postmeno. 12 Nullip. 1 Multip. 11 W—11, C—1	Bleeding 12 Discharge 12	Pain 7 Neg. 5	Fever 5 Neg. 7	Leucocytosis 3 Neg. 9			Culture—11 Not done—1 Anaerobes—3 Aerobes—4 Mixed—1 Neg.—3	Living—6 Not followed 6

TABLE II. PYOMETRA COMPLICATING SQUAMOUS CELL CARCINOMA OF THE CERVIX (WITH PREVIOUS RADIATION OR PREVIOUS OPERATIONS) (12 CASES)

HIST. NO. RACE—AGE PARITY	CLINICAL SYMPTOMS				ASSOCIATED DISEASES	OPERATIVE FINDINGS (C.C. PUS)	BACTERIOLOGIC FINDINGS	PREVIOUS RADIATION	TYPE OF PREVIOUS OPERATIONS	FOLLOW UP
	VAGINAL BLEEDING AND DISCHARGE	PAIN	FEVER	LEUCOCYTOSIS						
93237 W—62 yr. 1-0-1	+	+	–	–	Bromidism atrophic ext. genitals	10	No growth	–	Numerous dilatations and curettages	0
75644 W—51 yr. 5-0-5	+	+	–	–	–	40	Not done	X-ray Radium	Radium intracervical	Living
79312 W—59 yr. 8-0-6	+	–	–	+	Chr. cervitis c̄ cervical adhesions	50	No growth	X-ray	–	0
17238 W—71 yr. 4-0-3	+	+	+	–	Senility frequency	20	E. coli commun. anaerobic cocci, diph. bacillus	X-ray Radium	Radium intracervical	Living
A18074 W—51 yr. 5-0-4	+	+	–	–	0	20	Mixed anaerobes diph. bacillus	Radium	Radium intracervical	Living
A13493 C—69 yr. 1-1-0	+	–	–	–	Atrophic ext. genitals, vagina, cervix	30	Mixed anaerobes staph. albus diph. bacillus	Radium X-ray	Dilatation and curettage radium intracervical	0

A29684 W—26 yr. 2-0-2	+	+	−	−	0	10	Anaerobic cocci	X-ray	−	Died
A33662 W—66 yr. 11-4-7	+	−	−	−	R.V.O.	8	No growth	X-ray	−	Died
A53429 W—38 yr. 6-0-3	+	+	−	+	Papilloma of vagina	25	Anaerobic cocci, staph. albus, strep. hem., grp. B	X-ray Radium	Dilatation and curettage, conization cervical, radium intracervical	Living
A45035 W—43 yr. 3-0-3	+	−	+	−	−	20	Anaerobic cocci	X-ray Radium	Radium intracervical	Died
A35199 W—44 yr. 5-1-3	+	−	+	−	−	20	Strep. viridans diph. bacillus	X-ray Radium	Radium intracervical	Living
A72755 W—54 yr. 12-2-7	+	+	−	−	R.V.O. Senile chgs. genitals	10	Anaerobic cocci	X-ray	−	Living
Multip. 12 W. 11 C. 12 Postmeno. 7 Menstr. 5	Bleeding 12 Discharge 12	Pain 7 Neg. 5	Fever 3 Neg. 9	Leucocytosis 2 Neg. 10			Not done—1 Neg.—3 Anaerobes—3 Aerobes—1 Mixed—4	X-ray 10 Radium 7	Dilatation and curettage—3 Intracervical radium—7 Conization—1	Living 6 Died 3 No follow up 3

TABLE III. PYOMETRA COMPLICATING ADENOCARCINOMA OF THE UTERUS (5 CASES)

HIST. NO. RACE—AGE PARITY	CLINICAL SYMPTOMS				ASSOCIATED DISEASES	OPERATIVE FINDINGS (C.C. PUS)	BACTERIOLOGIC FINDINGS	PREVIOUS RADIATION	TYPE OF PREVIOUS OPERATION	FOLLOW UP
	VAGINAL BLEEDING AND DISCHARGE	PAIN	FEVER	LEUCOCYTOSIS						
47477 W—65 yr. 1-0-1	+	+	–	–	Cystitis senile vaginitis	50	No growth	X-ray	Dilatation and curettage	Living
A42196 W—80 yr. 0-0-0	+	–	–	–	Stenosed upper vagina, retroverted uterus, senile genital changes	150	No growth	–	Dilatation and curettage	Living
93092 W—55 yr. 6-1-5	+	+	+	+	Senility, atrophic arthritis, anemia, abdominal ascites	200	Anaerobic mixed organisms strep. gamma	Rad.	Radium intrauterine	Died
74666 W—56 yr. 5-0-2	+	+	–	–	Atrophic external genitals	20	No growth	Rad.	Uterus packed radium intrauterine	Died
A78440 W—54 yr. 9-0-6	+	–	–	–	Obesity, ureteral stricture	150	Anaerobic cocci	Rad. and x-ray	Dilatation and curettage radium intrauterine	Living
Postmeno. 5 Nullip. 1 Multip. 4 W—5; C. 0	Bleeding 5 Discharge 5	Pain 3 Neg. 2	Fever 1 Neg. 4	Leuco. 1 Neg. 4			Negative 3 Anaerobic 1 Mixed 1	X-ray 2 Radium 3	Dilatation and curettage 3 Radium 3 Ut. packed 1	Living 3 Died 2

TABLE IV. PYOMETRA (FOLLOWING CERVICAL OR UTERINE OPERATIONS) (4 CASES)

HIST. NO. RACE—AGE PARITY	CLINICAL SYMPTOMS: VAGINAL BLEEDING AND DISCHARGE	PAIN	FEVER	LEUCOCYTOSIS	ASSOCIATED DISEASES	OPERATIVE FINDINGS (C.C. PUS)	BACTERIOLOGIC FINDINGS	TYPE OF OPERATIONS (PREVIOUS)	FOLLOW UP
11191 W—52 yr. 11-0-9	+ +	−	−	−	Laceration of perineum; cystocele; rectocele chr. cervicitis; Lac. cervix	30	No growth aerobic only	Dilatation and curettage	Well
94816 W—51 yr. 9-3-1	− +	−	−	−	Cystocele, rectocele	50	Strep. viridans diph. bacillus	Removal of cervical polyp, repair 3° laceration	Well
A13493 W—47 yr. 6-1-4	− +	+	−	−	Endocervicitis, menorrhagia, trichomoniasis, stenosis of cervix.	10	Anaerobic cocci	Cauterization of cervix	Well
A4111 W—44 yr. 9-5-3	− +	+	+	+	Perineal tear, R.V.O., c̄ small cystocele and rectocele, sl. cervicitis, pruritus vulvae	25	Anaerobic cocci	Cauterization of cervix	Well
Postmenopausal 3 Menstr. 1 Multip. 4; W. 4	Bleeding 1 Neg. 3 Discharge 4 Neg. 0	Pain 2 Neg. 2	Fever 1 Neg. 3	Leucocytosis 1 Neg. 3			Aerobes 1 Anaerobes 2	Dilatation and curettage 1 Caut'r. 2 Removal polyps 1	Well 4

TABLE V. SPONTANEOUS PYOMETRA (NO CARCINOMA, PREVIOUS OPERATIONS OR RADIATION THERAPY) (15 CASES)

HIST. NO. RACE—AGE PARITY	CLINICAL SYMPTOMS					ASSOCIATED DISEASES	OPERATIVE FINDINGS (C.C. PUS)	BACTERIOLOGIC FINDINGS	FOLLOW UP
	VAGINAL BLEEDING	VAGINAL DISCHARGE	PAIN	FEVER	LEUCO-CYTOSIS				
71172 W—60 Yr. 0-0-0	+	+	+	–	–	Senile vaginitis, Strict. vagina, Myomat. uteri	8	Bacillus pyo-cyaneus	0
17238 W—53 Yr. 8-1-7	–	+	+	–	–	Minimal cervicitis	5	Mixed anaerobic cocci, piph. bacillus	Well
96900 W—55 Yr. 11-0-9	–	+	+	–	–	Pyelitis, Cystitis, Urethritis	50	Streptococcus hemolyticus, grp. B.	Well
82254 W—60 Yr. 0-0-0	–	+	+	+	+	Senile vaginitis ⁊ constriction Rheumatism	25	Not done	Well
75802 W—65 Yr. 8-2-7	+	+	–	–	–	Atrophic ext. genitals, vagina & cervix	40	No growth (aerobic only)	Well
80258 C—54 Yr. 13-2-11	–	+	–	–	–	Cervicitis c̄ Atrophy	40	No growth (aerobic only)	0
59360 W—57 Yr. 0-0-0	–	+	–	–	–	Senile genitals	10	E. coli communior	Well
88789 W—74 Yr. 11-1-8	–	+	+	+	+	Vaginitis	100	Anaerobic cocci	Well

37050 W—70 Yr. 6-0-6	+	+	−	−	−	Cystocele Rectocele, decensus uteri	20	Streptococcus hemolyticus, grp. A	Well
A60223 W—71 Yr. 7-2-7	−	+	+	−	+	Senility Arthritis rt. shoulder	10	Strep. viridans Strep. gamma	0
A63429 W—57 Yr. 9-0-8	+	+	−	−	−	Acute cervicitis	15	Anaerobic cocci	0
A71408 C—62 Yr. 11-0-6	+	+	+	+	−	Senile genitals	15	Anaerobic cocci	Well
A29684 C—55 Yr. 1-1-0	+	+	+	−	−	Senile genitals	20	Anaerobic cocci	0
A51870 W—42 Yr. 13-2-7	+	+	−	−	−	Completely stenosed cervix Nursing 18 mos. infant	20	Anaerobic cocci	Well
A83632 C—55 Yr. 0-0-0	−	−	−	−	−	Completely stenosed cervix	10	Anaerobic cocci	Well
Postmeno.—14 Menstr.—1 Nullip.—4 Multip.—11 W—11; C—4	Bleeding 7 Negative 8	Discharge 14 Neg. 1	Pain 8 Neg. 7	Fever 3 Neg. 12	Leucocytosis 3 Neg. 12			Not done 1 Anaerobic 7 Aerobic 5 Mixed 2	Well—10 Not Followed 5

For broth culture of the anaerobes a medium using neutralized beef heart as described by Lepper and Martin[34] was found most satisfactory.

Clinical Grouping of Patients.—Tables I to V show our clinical grouping of the patients.

Bacteriologic Findings.—The complete cultural findings in the pus from 39 patients with pyometra are shown in Table VI. Cultures of the pus from 8 patients showed no growth. Sterile cultures from pyometra were most common in patients with adenocarcinoma of the uterine corpus. No culture was sterile in the "spontaneous" group with pyometra.

TABLE VI

	MIXED ANAEROBIC COCCI	MIXED AN-AEROBIC COCCI AND ANAEROBIC BACILLI (NO SPORES)	MIXED AEROBIC AND ANAEROBIC ORGANISMS	AEROBIC ORGANISMS	NO GROWTH
Spontaneous pyometra (no carcinoma, previous radiation or operations)	5	0	2	5	0
Pyometra (following operations on the cervix uteri)	2	0	0	1	0
Pyometra complicating carcinoma of cervix (no previous radiation or operations)	1	2	1	2	2
Pyometra complicating carcinoma of cervix (previous radiation or operations)	3	0	4	1	3
Pyometra complicating adenocarcinoma of uterus	1	0	1	0	3
Totals	12	2	8	9	8

DISCUSSION OF BACTERIOLOGIC FINDINGS

Anaerobic Infection.—Early in this study attempts were made to group the various strains of anaerobic cocci by the method advocated by Colebrook,[35] who used colony formation as a basis for grouping. It was found that a grouping of this type was unsatisfactory. Pure culture studies showed that the term "anaerobic streptococci" for the group as a whole was a poor one. Morphologically, many strains resembled more closely staphylococci. Growth was easily obtained in the mixed cultures or in symbiosis. Separation and propagation of *individual*

strains were more difficult and often impossible. We feel that much further work must be done on methods of culture within this group before any method of classification of the group as a whole has practical significance.

The term *"anaerobic"* as used means obligate anaerobiosis. All microaerophilic strains, or strains which grew aerobically after several transplants, were classed as aerobes. The term "anaerobic cocci" means in general a mixture of cocci, streptococci, and diplococci. The term "mixed anaerobes" means that with the cocci were mixed various types of anaerobic nonspore-forming bacilli.

In 39 complete cultures anaerobic organisms were found in 22. In 12 cultures anaerobic cocci were found alone; in 2 cultures they were found with anaerobic bacilli; in 8 cultures they were in symbiosis with aerobic organisms.

Aerobic Infection: Purely aerobic organisms were found in 9 cultures. In 8 other cultures they were found in symbiosis with anaerobic organisms.

Streptococcus hemolyticus (Group B, Lancefield) was isolated twice, once in pure culture and once in symbiosis with *Staphylococcus albus* and with anaerobic cocci. *Streptococcus hemolyticus* (Group A, Lancefield) was isolated once in pure culture.

E. coli communior was isolated once in pure culture and *E. coli communis* once in symbiosis with anaerobic cocci and with a diphtheroid bacillus.

Diphtheroid bacilli were found 9 times in symbiosis and once in pure culture.

Aerobic nonhemolytic streptococci were found 3 times in symbiosis with other organisms.

Streptococcus viridans was found in symbiosis in 3 cultures.

Staphylococcus aureus was found once in pure culture and twice in symbiosis with other organisms.

Bacillus pyocyaneus was isolated once in pure culture.

CONCLUSIONS

From analysis of this small series no definite conclusions can be drawn. Since anaerobic organisms, capable of invading the cervix and uterine cavity are found normally in the vaginas of postmenopausal women in a higher incidence than in the vaginas of childbearing women, the possibility of endogenous infection must be considered. When nonhemolytic streptococci, diphtheroid bacilli, *Streptococcus viridans, Staphylococcus albus,* and bacilli of the colon group are cultured in pyometra, endogenous infection may be predicated. On the other hand the culture of *Streptococcus hemolyticus* (especially Group A) and *Staphylococcus aureus,* neither of which is commonly found in the vagina, argues against endogenous infection.

Whether infection is necessary in the production of "spontaneous" and "operative" pyometra can only be determined by careful culture of a large number of pyometra patients. In this small series *sterile* pyometra occurred most commonly in uteri with adenocarcinoma and in uteri with squamous cell carcinoma of the cervix before and after irradiation therapy. No culture was sterile in the "spontaneous" group with pyometra.

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DISCUSSION

DR. HARVEY B. MATTHEWS, Brooklyn, N. Y.—At the Long Island College Hospital we have encountered pyometra 25 times in the past seventeen years. The records of three patients were not available and hence this report will include only 22 cases. Dr. Carter's grouping is excellent, and we have used it in collecting our data. There are 5 groups as follows:

	NO. CASES
1. Pyometra complicating squamous cell cancer of cervix (no previous operations or radiation)	0
2. Pyometra complicating squamous cell cancer of cervix (with previous radiation or operation)	6
3. Pyometra complicating adenocarcinoma of the uterus (without previous radiation or operation)	2
4. Pyometra following cervical or uterine operations	6
5. "Spontaneous" pyometra (no carcinoma, previous operation or radiation therapy)	8
Total cases	22

Until recently only aerobic cultures were routinely done as in most hospitals and therefore many cultures from pyometra were reported negative. However, our material showed positive cultures in 8 cases and no growth in 4 while no cultures were taken in 10 cases, none of these latter being recent. Four out of the 8 positive cultures and 2 out of the 4 negative cultures were anaerobic growths. It would seem therefore that cultures should always be grown both under aerobic and anaerobic conditions, for otherwise too many negative cultures will be reported.

With reference to sterile pyometra in carcinoma of the cervix, one-half of our 6 patients who had had previous radiation were sterile, and of 2 cases of carcinoma of fundus after previous operation or radiation, one patient was sterile and one was not cultured. I mention this because we had the idea, and I think most men have, that pyometra in the presence of cancer is always infectious.

In conclusion, I would like to emphasize the fact that in any study of the bacteriology of pyometra, all cultures must be grown under both aerobic and anaerobic conditions, otherwise results will be obtained that are not reliable. This is also most important when considering treatment.

DR. JOHN A. McGLINN, PHILADELPHIA, PA.—In order to have pyometra we must have three things: discharge, failure of drainage of the uterus, and infection. We find most of these cases among the malignant group, and next in order those among the senile group where we have obstructive lesions around the cervix and vagina. Formerly we saw quite a few of these cases due in part to faulty surgery. I can recall such cases following trachelorrhaphy, where we would fail to preserve the cervical canal for drainage.

I once made the statement that many of these cases were due to indiscriminate and faulty cauterization of the cervix, and have been taken to task for saying this. I have, however, a case of endocervicitis of my own treated by cautery that developed a hematometra and subsequently a pyometra. I attempted to maintain the patency of the cervix but failed and another surgeon eventually removed the uterus. I have also removed the uterus of another patient who had been cauterized by another physician with resultant pyometra.

Irradiation also plays a part in developing a stenosis. I do not think it occurs very frequently, because there is usually one factor missing, namely the discharge, but stenosis does occur. This brings up the point that we should be a little more careful in irradiating these so-called benign bleedings. In benign bleeding before the menopause I have long discarded the use of radium, and I have not had enough faith in hormones to control menopausal symptoms. In those cases which are postmenopausal, it is only anticipating what Dr. Scheffey may say in the next paper, to state that radium does not give protection against the later development of cancer. It has been my practice for some time in dealing with a woman who is past the menopause to remove the uterus entirely by the vagina.

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—Gynecologists may be aware that there are two longitudinal ridges within the cervix but I have never heard them mentioned by any clinician or pathologist. The two ridges, usually located asymmetrically, anteriorly and posteriorly, tend to extend the entire length of the canal and, quite similar to the turbinates of the nose, are subject to very marked hypertrophy. Cysts so frequently encountered in the region of the internal os usually develop in the upper end of a hypertrophic longitudinal ridge. These ridges are important factors in the development of primary cervical obstruction and obstruction complicating endocervical therapy. It is, therefore, quite evident that these longitudinal ridges play a significant part in the etiology of pyometra.

DR. RAYMOND E. WATKINS, PORTLAND, OREGON.—Inasmuch as pyometra is so frequently associated with carcinoma of the uterus, it becomes a complication

which gives us a great deal of concern in the treatment of cancer. In reviewing our cases I have found that we had 17 patients with pyometra in the last eleven years. Eight of these were associated with carcinoma.

I recently visited a clinic in New York, and found that they ordinarily disregard pyometra, proceed with the placing of radium in the endometrial cavity, and only remove it in case the patient has a very high temperature reaction. We tried this plan, but there have been one or two severe reactions. While Dr. Carter has not discussed the treatment in any way, I would like to hear an expression from him regarding the management of pyometra, particularly previous to irradiation.

DR. CARTER (closing).—The practical nature of our findings will help to answer Dr. Watkins' question. We feel that pyometra should be suspected in the patients with squamous cell carcinoma of the cervix and in patients with adenocarcinoma of the corpus. We feel that it is safe following drainage to start x-ray therapy, but we should be most hesitant to insert radium into the cervical canal or into the corpus in the presence of infection without proper drainage for an appreciable time.

In our 39 patients with pyometra, anaerobic organisms were found in 22. In 8 other cultures, anaerobic organisms were found in symbiosis with aerobic organisms. Purely aerobic organisms were found in 9 cultures and in 8 other cultures were found in symbiosis with anaerobic organisms. We believe that the administration of x-ray therapy can be instituted safely provided the usual principles of maintenance of drainage and careful bacteriologic and clinical checking of the patient are followed.

The same problem arises in the patients with spontaneous pyometra. From our material it is seen that no culture was *sterile* in spontaneous pyometra. Following the drainage of spontaneous pyometra, we feel that curettement should be delayed over a period of weeks. We also feel that bacteriologic following is most important in determining when the curettement for diagnostic purposes should be done.

Bacteriologic checking of the patients is easily done by smear and culture methods by independent laboratory workers. This checking stresses the close correlation between the initial and subsequent bacteriologic findings.

The anaerobic organisms are poorly understood. They are difficult organisms with which to work. We feel that the term, "anaerobic streptococci," for the group as a whole is a poor term. Morphologically many strains resemble staphylococci. Separation and propagation of individual strains are difficult and, at times, impossible procedures.

Judgment as to the time to use the curette, radium, or x-ray following the evacuation of pyometra is difficult. Bacteriologic findings should help in answering some of the problems.

THE EXPERIMENTAL PRODUCTION OF TOXEMIA OF PREGNANCY*

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(From the Department of Obstetrics and Gynecology, University of Chicago)

THE present experiments represent an attempt to demonstrate under conditions of laboratory control, the production in rabbits of the anatomic lesions which characterize uteroplacental apoplexy in women. Uteroplacental apoplexy, in the words of Couvelaire (1911) who named it, is characterized by "a colossal infiltration of blood in the uterine wall, occurring in the region of attachment of the membranes as well as in the region of placental attachment, cleaving the muscle bundles and dissociating certain bundles fiber from fiber. The ovaries are riddled with points of hemorrhagic effusion. The broad ligaments are infiltrated with blood. It amounts indeed to a veritable 'apoplexie utero-placentaire.'" The present experiments therefore involve the production of hemorrhage into the wall of the uterus and placenta which results frequently in premature separation of the placenta.

Since injury of this type occurs in women under conditions of obscure etiology, the present problem is: first, to determine whether or not identical anatomic lesions occur in a laboratory animal, and second, to evaluate the various factors introduced under controlled experimental conditions which cause normal pregnancy to terminate in uteroplacental apoplexy.

METHOD AND MATERIAL

The present series includes 34 rabbits in which the course of pregnancy was experimentally altered by the injection of an extract of the urine of pregnancy, antuitrin-S (Parke, Davis and Co.), usually at twenty-five days which is the beginning of the last quarter of gestation. By this means ovulation was induced about the twenty-fifth day of pregnancy, so that at the normal end of gestation at thirty-two days there was present in the ovaries a fresh set of corpora lutea which had reached the stage of maximal size and function. The application of this method to the analysis of the factors concerned in parturition has been tested in previous investigations and the general nature of the anatomic abnormalities which were encountered in the uterus and placenta have been described (Snyder, 1934, Snyder and Deitrick, 1935, Snyder, 1938, 1939, Snyder and Koteen, 1939).

OBSERVATIONS

Macroscopic Appearance.—In the present series of animals, the uterus was the site of gross anatomic changes. In a typical instance, dark

*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

purple areas of discoloration completely encircled the uterus at certain regions and extended far into the broad ligament (Fig. 2). The margins of the dark patches were irregular in outline and less deeply col-

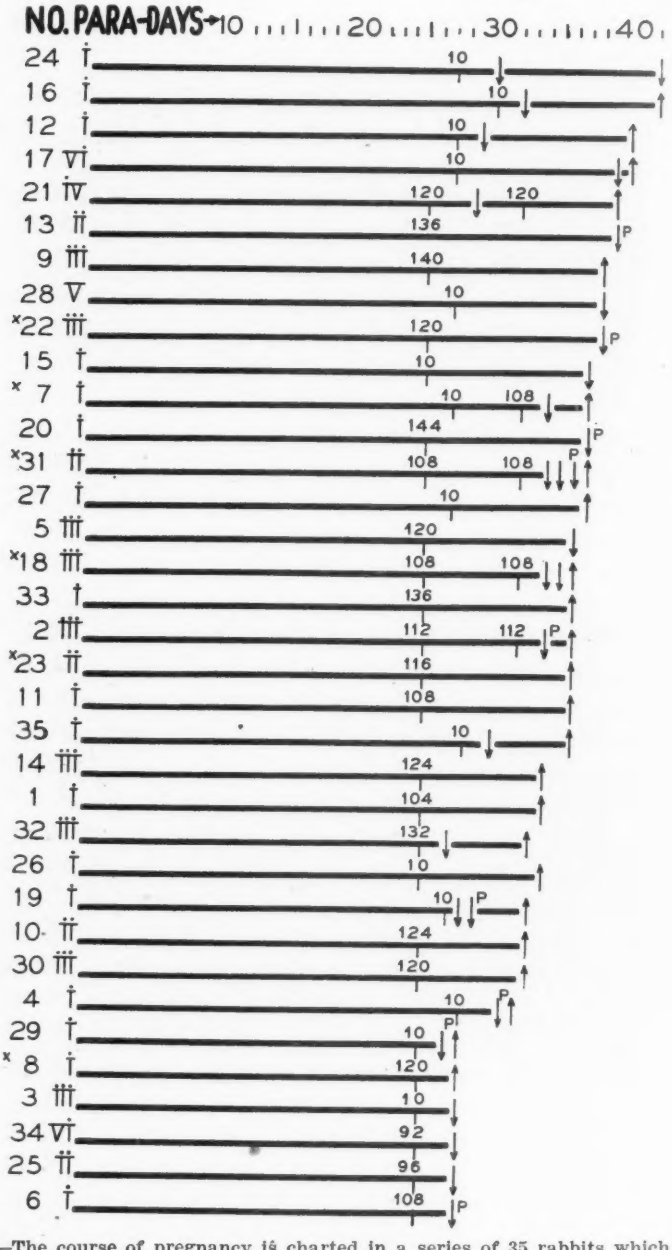

Fig. 1.—The course of pregnancy is charted in a series of 35 rabbits which showed hemorrhagic lesions of the uterus, such as characterize uteroplacental apoplexy in women. Each case is summarized, giving the time of injection of urine extract (antuitrin-S), the total dosage in rat units, and time of delivery. Complete emptying of the uterus is indicated by downward arrow with *P;* extrusion of part of a litter by downward arrow; delivery by hysterotomy by upward arrow. Maternal death during the experiment is shown by *X.* Of a total of 108 fetuses expelled before 36 days, 75 of them were born alive.

ored. Close inspection of the muscle layer of the wall showed strands which were distinguished by their pale color in contrast to the dark background caused by hemorrhage. There was actual separation of bundles of fibers by the dark-colored hemorrhagic extravasations which were wedged between them. Localized pressure with a finger tip failed to cause blanching, thus revealing that there was infiltration of the

Fig. 2.—Uteroplacental apoplexy. Animal 14 sacrificed ante partum at first sign of external vaginal bleeding; 34 days, 6 living fetuses.

Fig. 3.—Infiltration of blood into the uterine wall involving the region of placental attachment. Animal 29, sacrificed following the birth of 10 living fetuses at 27 days.

uterine wall rather than a mere engorgement with blood retained within the vessels. In the region of the implantation site, the hemorrhagic extravasation was especially dense and frequently extended into the adjacent broad ligament (Fig. 3).

Incision of the uterus in the region of discoloration showed that all three layers of the uterine wall were involved in the hemorrhagic

extravasation. In certain areas the hemorrhage into the tissues was so dense that the boundaries between layers were obscured, and the wall appeared homogeneous. Blood was frequently encountered within the uterus, having escaped to the region between the fetal membranes and the mucosa. The extramembranal hemorrhage could be seen directly through the thin uterine wall in many instances. Displacement of the blood promptly followed both the application and release of localized pressure upon the uterus, which thus aided differentiation from intramural bleeding. On opening the amniotic sac, blood-stained fluid was noted at times, but less frequently than extramembranal hemorrhage. In the lungs of fetuses which had died before delivery by hysterotomy, blood was readily demonstrated, and widely distributed throughout the alveoli (Snyder, 1940).

On cutting through the placenta, areas of hemorrhagic infiltration of the tissues were found. The maternal part of the organ was conspicuously involved. In the retroplacental region, the extravasation of blood could be linked with partial separation of the placenta from

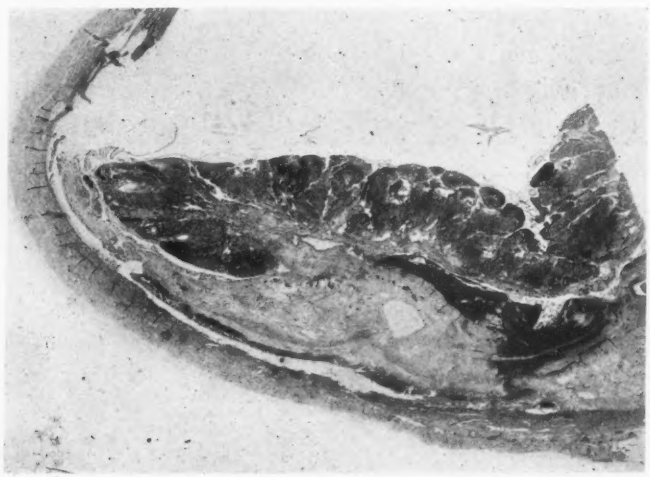

Fig. 4.—Hemorrhagic infiltration of the placenta. Animal 11, sacrificed ante partum; 36 days, 4 postmature fetuses.

the uterine wall (Fig. 4). The escape of blood in the retroplacental area extended beyond the placental margin, and was continuous with the hemorrhage separating the fetal membranes from the decidua vera (Fig. 5).

Incision of the broad ligament showed especially dense infiltration of blood in the loose connective tissue between the folds of the mesometrium.

Upon first opening the peritoneal cavity, an increase in the normal amount of peritoneal fluid was encountered, which was markedly stained with blood at times. The serosal region of the uterine wall was involved extensively and infiltration of blood was seen at many areas where the dark discoloration of intramuscular hemorrhage was not evident. A deep longitudinal fissure marked the site of rupture of the uterus in one animal in which a full-term fetus escaped into the peritoneal cavity.

Microscopic Examination.—In the animals of the present series the extravasation of blood into the decidual, muscular, and serosal regions

of the uterine wall has been verified by microscopic examination. Correlation of the histologic findings with the functional changes of the uterus may be illustrated by specific cases.

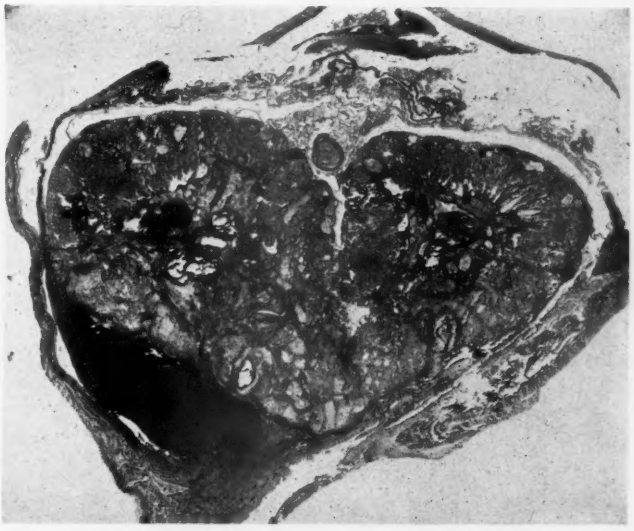

Fig. 5.—Partial separation of the placenta; retroplacental hematoma and escape of blood between the membranes and uterine mucosa. Animal 7, died at 37 days; 6 postmature fetuses in the uterus, 2 others having been expelled at 34 days.

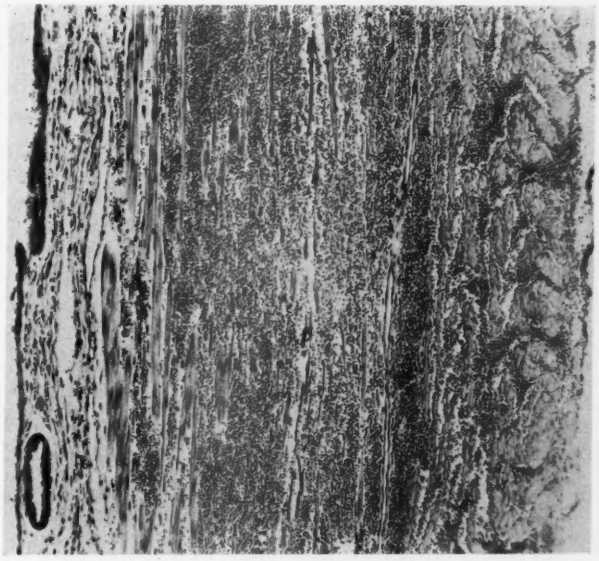

Fig. 6.—Wall of uterus showing hemorrhagic infiltration (Animal 14).

In an animal (No. 14) which was sacrificed at the first appearance of external vaginal bleeding at thirty-four days, and before the birth of any fetuses, the uterus contained six postmature fetuses which showed active movements. A transverse section taken through the entire uterus

and placenta, when stained with eosin and hematoxylin presented a brilliant picture even to the unaided eye, illustrating the extensive hemorrhage into the tissues (Fig. 2). The lateral wall showed dense infiltration of the serosal and muscular regions (Fig. 6). Separation of bundles of muscle fibers by huge extravasations of blood was strik-

Fig. 7.—Separation of muscle fiber bundles (Animal 14).

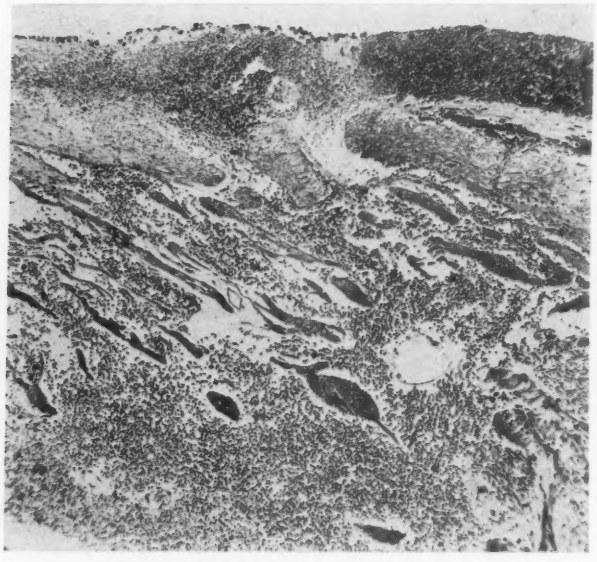

Fig. 8.—Broad ligament infiltration (Animal 14).

ing and was characteristic of the state of a large part of the uterine wall (Fig. 7). In connection with the escape of blood in the serosal layer, there was found in this animal a blood-tinged peritoneal fluid of excessive amount. The decidua vera was less extensively infiltrated than the other layers.

A section of the broad ligament revealed dense infiltration between folds of the mesometrium and in the serosal region (Fig. 8).

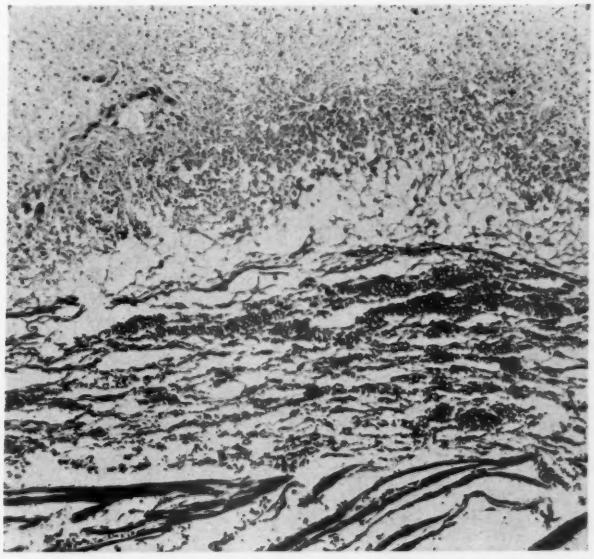

Fig. 9.—Retroplacental hemorrhagic infiltration (Animal 14).

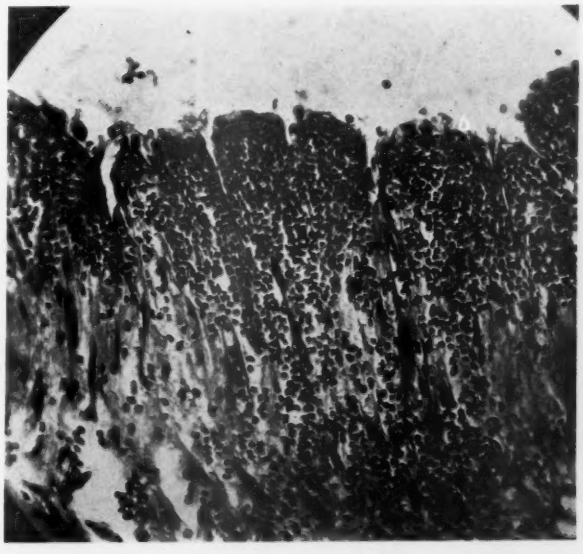

Fig. 10.—Perivascular infiltration. Animal 5, sacrificed at 36 days; 4 postmature fetuses expelled, 5 remaining in the uterus.

The site of the attachment of the placenta showed marked infiltration of red blood cells which was limited to the zone of connective tissue interposed between the maternal placenta and the muscle layer of the uterus (Fig. 9). Sections of the maternal placenta of this animal (No. 14) did not show hemorrhagic infiltration. The escape of blood

was evident, extending from the margin of the placenta laterally between the surface of the decidua vera and the membranes which were reflected by it.

Hemorrhagic infiltration of the maternal portion of the placenta was illustrated in an animal (No. 11) sacrificed at thirty-six days. None of the litter had been born and no external vaginal bleeding was noted. The four fetuses which occupied a single horn of the uterus were dead but not macerated, and their stage of development was the maximal attained during intrauterine life. Extravasation of blood extended from the muscular layer of the uterus through the entire thickness of the maternal portion of the placenta (Fig. 4). Partial separation of the placenta associated with a striking retroplacental hematoma was clearly shown in Animal 11. The animal (Fig. 5) was found dead on the thirty-seventh day. Two stillborn postmature fetuses had been expelled and 6 additional fetuses of excessive size remained in the uterus.

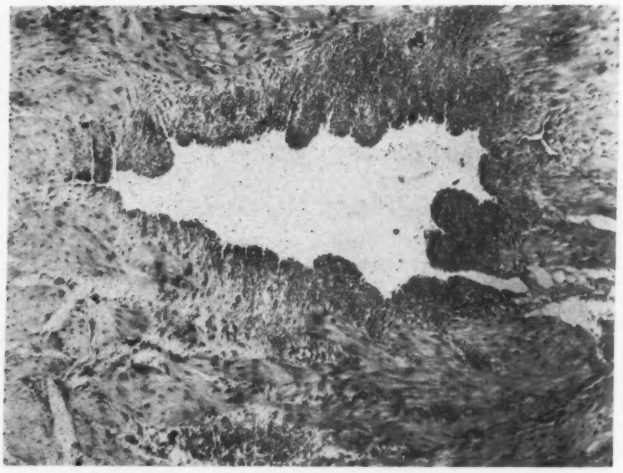

Fig. 11.—Perivascular and myometrial infiltration (Animal 5).

Hemorrhagic infiltration of the implantation region was evident in Animal 29 which was sacrificed at twenty-eight days (Fig. 3). The entire litter of immature fetuses was expelled alive at twenty-seven days. Microscopic examination revealed dense extravasations, especially involving the decidual layer in the region of the placental attachment. Various stages in the partial dislodgment of the placenta associated with decidual extravasations may be found by sacrifice of animals before completion of labor.

Blood vessels were also the site of infiltrations of red blood cells in the perivascular area (Fig. 10). In Animal 5, sacrificed at thirty-six days, 4 large, postmature fetuses had been stillborn and 4 additional fetuses remained unexpelled. A dense extravasation of blood occupied the perivascular sheath and at certain areas extended into the myometrium (Fig. 11).

To summarize briefly, the anatomic lesions in the uterus were characterized by hemorrhage into the uterine wall, involving all three layers. Throughout the entire decidual lining of the uterus, extravasa-

tions were found, both in the stroma of the retroplacental region as well as outside of this area, i.e., in the decidua vera. The maternal portion of the placenta is frequently a site of extravasation of blood which may result in partial separation of the placenta from the uterus. In the muscle layer the escape of blood into the tissue was linked with the separation of bundles of fibers over the entire circumference of the wall in certain regions. In the serosa, outpouring of blood is likewise extensive.

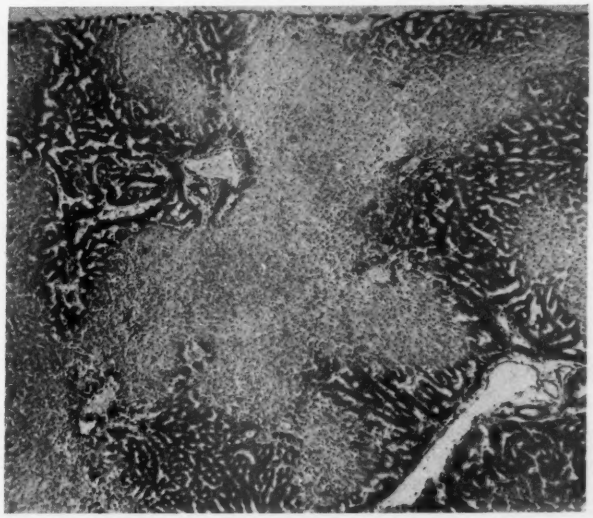

Fig. 12.—Liver necrosis. Animal 18, died at 36 days; 6 postmature fetuses expelled, 1 remaining in the uterus.

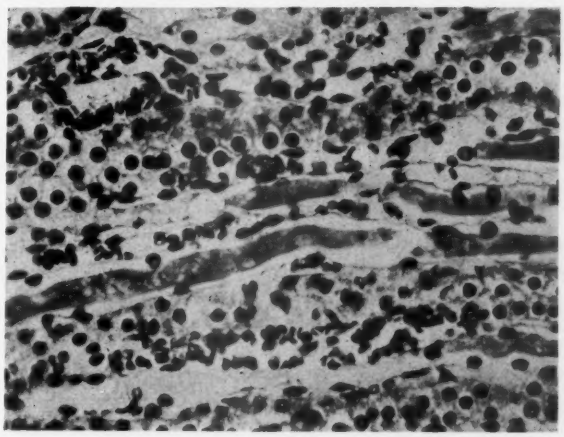

Fig. 13.—Kidney containing casts (Animal 5).

Histologic examination of other organs obtained at autopsy revealed clearly that injuries involved other tissues besides the generative tract. Striking changes were found in the liver, kidneys, lungs, and other organs. For example, in Animal 18 which died at thirty-six days following birth of 5 postmature fetuses, the liver showed extensive areas

of necrosis (Fig. 12). In Animal 5, which was sacrificed at thirty-six days during labor, as previously described, there was widespread damage of the kidneys (Fig. 13). The death of 6 animals of the total of 34 rabbits in the course of experimentally altered pregnancy was direct evidence of the magnitude of the functional injuries.

RELATION OF PHYSIOLOGIC TO ANATOMIC CHANGES

The physiologic changes are no less striking than the anatomic alterations which accompany induction of ovulation. Functional disorganization of labor as shown by either inhibition of parturition or by the premature expulsion of fetuses is linked with structural injury which may involve the entire uterine wall. A notable feature, however, is the birth of living offspring despite these conspicuous abnormalities. Thus, an indication is given of the narrow margin which separates the physiologic from the pathologic consequences of pregnancy.

In the present series of animals, a single injection of an extract of urine of pregnancy, antuitrin-S (Parke, Davis and Co.), about the beginning of the last quarter of gestation, resulted in the induction of ovulation. In the presence of a fresh set of corpora lutea in the ovaries, normal parturition at term failed to occur. The time of onset of parturition may be either postponed or hastened, the reaction being determined by the dosage and by the stage of pregnancy at injection. These factors may be adjusted so that in a given animal both types of response can be elicited; certain fetuses in a litter may be cast out prematurely and alive, while the rest of the litter survives in the uterus and eventually attains postmature stages of development.

In connection with the control of the duration of gestation in the rabbit by the induction of ovulation, it is especially noteworthy that the change in the time of onset of parturition, whether postponing the termination of pregnancy or hastening it, still followed a definite pattern. Emptying of the uterus occurred either at the beginning of the sixteen-day life span of the induced corpora lutea or at the end of it. Since living fetuses were born when pregnancy was interrupted by this method, the procedure offers the functional equivalent of spontaneous parturition. The normal mechanism of labor seems to be in operation except at an earlier or later time than is usual. The duration of pregnancy may be formulated in terms of hormonal function.

The striking physiologic alteration of the course of pregnancy prompted investigation of the anatomic basis of parturition under these conditions. Examination of the uterus in animals in which parturition set in on the second or third day following injection revealed striking changes in the decidua. The escape of blood from the vessels and infiltration of the area of attachment of the placenta was associated with the accumulation of blood between the membranes and the surface of the decidua vera. At the margin of the placenta, hemorrhage was conspicuous. Dense retroplacental extravasation of blood resulted in partial separation of the placenta from its site of attachment. The origin

was revealed of the vaginal hemorrhage of fresh blood which preceded the expulsion of living fetuses by hours in some cases. Similarly there was evidence of the structural changes associated with excessive postpartum hemorrhage which frequently occurred.

Since the birth of living fetuses occurred in the course of induced labor by this method, there remains to be considered in addition to the decidual changes, a second factor, namely, the state of contractility of the uterine muscle. In this connection it was noted upon examination of the uterus that while certain placental areas were the sites of hemorrhagic extravasations which result in dislodgment of the product of conception, the rest of the implantation areas of a litter were not involved. The fetuses remaining in the uterus continued to grow to extreme stages of postmature development, being finally cast out at the the end of the life span of the induced corpora lutea. The fact of the survival of the fetuses which were implanted adjacent to those which were cast out alive was direct evidence of the relatively quiescent state of the uterine muscle, although still functioning adequately for the expulsion of living offspring. Dislodgment of certain fetuses of a litter was not caused by muscle contraction alone but was related to structural changes of the decidua, involving the placenta. Induction of parturition was effected by means of induced premature separation of the placenta rather than by a muscle response.

At this point one may pause to recall a general principle with regard to the relation of the ovary to the uterus in all mammals, namely, that the development of a fresh set of corpora lutea is invariably linked with structural changes of the uterus involving hyperemia and growth (Swezy, 1935). Since ovulation can be induced experimentally in the rabbit during pregnancy at any time which is desired (Snyder and Wislocki, 1931), it is evident that the pregnant uterus may be subjected to increase in the stimulus which normally results in hyperemia, the magnitude of the increase being of such amount as is afforded by the addition of a fresh set of corpora lutea in the ovaries.

The question also arises as to what state of functional activity of the uterine muscle was associated with the intramuscular extravasation of blood. Hemorrhagic infiltration of the muscular layer was a striking feature of the uterus in which full-term or postmature development had been reached under the present experimental conditions. Functionally, there was failure of the uterus to expel its contents at term; uterine inertia was marked. Examination of the ovaries revealed a fresh set of corpora lutea at the stage of full development. Evidence that the induced set of corpora lutea were functional was afforded not only by the quiescent state of the uterine muscle but also by other findings (Snyder, 1934): (1) Absence of pituitrin effect; pituitrin administered at term failed to induce parturition despite a dosage 1000 times greater than the amount normally effective. (2) Absence of ovulation after coitus; the period of inhibition of ovulation which normally ended at

term was prolonged a week past term. (3) Microscopic examination of the ovaries and uterine mucosa of the nonpregnant horn in unilateral pregnancy; there were changes characteristic of active corpora lutea.

The survival of the fetuses within the uterus following inhibition of parturition and their attainment of extreme stages of postmature development afforded additional evidence of the functional state of the decidua and placenta. Furthermore, after the limit of intrauterine survival was reached at thirty-five days, the dead fetuses were not cast out at once but usually were retained within the uterus until about the forty-first day or the end of the life span of the induced set of corpora lutea. Thus, the outstanding physiologic change in the uterus at term and during postmaturity involved the musculature rather than the decidua. It was during this period likewise that the uterine musculature was involved conspicuously not only in functional change but also in striking anatomic lesions, namely, extensive hemorrhagic extravasations.

The time sequence in which the hemorrhagic extravasations appear as well as the difference in the site of bleeding in the layers of the uterine wall afford clues which aid in the attempt to trace the nature of the injury which marks the transition from the normal uterus to that of uteroplacental apoplexy. Under the conditions of the present experiments, the process of labor may be slowed down so that the duration of the period from the onset of expulsion of the first fetus until the extrusion of the last one of the litter is two weeks. The dissociation of the mechanism of labor followed a regular pattern and occurred in two phases. One period of the expulsion of fetuses was on the second and third days following ovulation; the second period of expulsion was about two weeks after ovulation. The two phases differed strikingly with regard to the changes which occurred in the uterine wall, although both led to the emptying of the uterus. In the first period, decidual changes predominated, and the muscular contractility was minimal; in the second phase muscular contractions were uninhibited, response to pituitrin had returned, and decidual changes were slight. In both periods of expulsion of fetuses, anatomic changes of the uterine wall readily passed beyond normal limits to the pathologic state characterized by extravasations of blood. Uteroplacental apoplexy involving premature separation of the placenta was thus associated with the mechanism of labor. Exaggeration of the normal mechanism to a pathologic state was illustrated in so far as the hemorrhagic lesions were not entirely irregular but occurred in a definite anatomic and chronologic pattern. In emptying of the uterus, two cardinal factors stand out, namely, the decidual and the muscular; evidence of their respective roles in parturition is obtained by attempting to exhibit them one at a time, since normally they are not dissociated.

In brief, starting with normal pregnancy, the anatomic and physiologic changes which characterize premature separation of the placenta

and uteroplacental apoplexy have been traced in relation to the labor mechanism; and in turn the pathologic processes have been linked with the endocrine regulation of gestation, especially the factors concerned in the duration of pregnancy.

RELATION TO CHANGES IN THE REST OF THE BODY

In women uteroplacental apoplexy has long been linked with far-reaching changes throughout the body. Upon the basis of clinical findings and the evidence obtained at autopsy, it has been regarded as a manifestation of toxemia of pregnancy. "Accidental hemorrhage is an intoxication of the same kind which causes albuminuria, eclampsism, or eclampsia" (Essen-Möller, 1913). "In accord with this view are found practically all who have studied the subject, among whom may be mentioned: Bar, Couvelaire, Williams, Smyly and Ley" (Willson, 1922). Fitzgibbon (1918) proposed the term "antepartum toxemic hemorrhage" for the disease. As the uterine lesion of the eclamptic type of toxemia, the significance of uteroplacental apoplexy was comparable to such striking changes as hemorrhagic hepatitis, extensive necrosis in the kidney, or hemorrhage into the brain. Schmorl's findings at autopsy were emphasized; namely, that eclampsia involved a more far-reaching disorder than could be defined by restricting it to symptom-like convulsions which often were not observed, as he noted, although the liver, kidneys, brain, and other organs might show well-marked lesions in women dying at the time of labor.

How to approach the reconstruction of toxemia in a laboratory animal has long been puzzling. The embryologic method involves tracing of the complex back to the rudimentary by taking earlier and earlier stages in the development of a structure or function. The problem is to reconstruct experimentally disorders of pregnancy which involve both function and structure, early as well as late pregnancy, occurrence in not totally irregular fashion and changes in the organism as a whole as well as in specific tissues.

The question is, what features of toxemia should one select for experimental analysis: convulsions, hypertension, albuminuria, edema, liver necrosis, kidney damage, or uteroplacental injury? Since all may be manifest in the same individual in the course of toxemia of pregnancy, a choice of any one appears to be rather arbitrary. If one turns from pathologic pregnancy to consider the factors chiefly concerned in the maintenance of the delicate physiologic balance of normal pregnancy, it is apparent that the mechanism of the sexual cycle is intimately involved. There is evidence that pregnancy is composed physiologically of a series of cycles which are not completely suppressed, the cycles being the functional units or links in the chain of events constituting pregnancy by which a timing mechanism is set at a given rate for a species (Snyder, 1938).

The cycle is under hormonal control. Experimental introduction of ovulation during pregnancy is a method for changing the hormonal coordination at various stages of pregnancy as desired, while keeping constant the endocrine pattern of the ovulation cycle. Experiment by this method may reveal whether or not the endocrine balance can be altered sufficiently to produce a modified pattern of pregnancy such as lengthening it or shortening it, or slowing certain phases such as parturition, while still preserving a physiologic outline. Increase in stimuli may be traced in terms of increased responses until finally the break in adjustment appears without loss of all physiologic relations. The sites of injury may be traced to exaggeration of the physiologic processes. Furthermore, the period of pregnancy at which the stimulus is introduced may be varied. Alteration of the hormonal or chemical coordination of pregnancy may thus result in abnormalities which vary according to the period of pregnancy and the intensity of the stimulus.

The systemic effects and involvement of visceral organs are ultimately connected with known experimental procedures, since in the beginning pregnancy was normal. Thus, there is evidence of the type of injury and the nature of the toxic process.

It is known that in many respects the embryo has a special physiology. To a considerable degree the maternal organism as well during normal pregnancy shows greatly altered reactions, especially in magnitude. The magnitude of the physiologic changes which characterize pregnancy in contrast to the nonpregnant state may be illustrated by the two extremes of response which are observed following injection of a drop of urine extract (antuitrin-S). In the immature rabbit there is little or no effect. In the pregnant animal injury may attain the proportions of general systemic involvment or intoxication resulting in death.

CONCLUSIONS

1. Uteroplacental apoplexy involving premature separation of the placenta was observed in rabbits following induction of ovulation by injection of urine extract (antuitrin-S) during pregnancy.

2. Anatomic evidence showed that injury attained the magnitude of general systemic changes or intoxication, resulting in death.

3. Physiologically, the genesis of the injury or nature of the toxic process was traced ultimately to alteration of the hormonal coordination of pregnancy.

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DISCUSSION

DR. ROBERT A. ROSS, Durham, N. C.—Dr. Snyder has studied the effect of pregnancy urine extract on the pregnant and nonpregnant uterus of rabbits and has noted gross and histologic changes in the pregnant uterus similar to the human uterus with uteroplacental apoplexy. He properly believes that these observations might aid in answering the problem of this condition in the human being.

Naturally one realizes the danger of interpreting animal experimentation in terms of the human being, and, in this particular study, one recalls the work of Evans and others which shows the highest titers of the gonadotropes to be at the second and third months of gestation. Also in the human being we know that only 50 per cent of cases of abruptio placentae have a toxemic background. In a study of 34 women who died in the eclamptic state and on whom complete autopsies were obtained, we found basophilism of the pituitary in only one instance and in this individual also was found hyperluteinization of the ovary. If a profound derangement of the endocrine system is constantly present in toxemias and if there is uniform increase in the gonadatropes, one might expect more histologic evidence than we found in these 34 women. The essayist's work is however, consistent with the conclusions of Smith and Smith which had to do with changes in the gonadatropes and estrogen in the toxemias.

DR. GEORGE VAN S. SMITH, Brookline, Mass.—Dr. Snyder has produced, experimentally, lesions similar to those of specific toxemia of human pregnancy. He has produced them by hormone deprivation.

The endometrium of the human being at the time of menstruation may be said to go through a process of apoplexy. The monumental work of Markee has led him to believe that the cause of the changes in the endometrium, before and at the time of menstruation, is a local factor resulting from hormone deprivation. In the menstrual discharge, we have found what appears to be a specific toxin which we believe explains the behavior of the endometrium following hormone deprivation.

We have found that urinary hormone changes similar to those before and at menstruation precede and accompany labor and also toxemia of late pregnancy, indicating that hormone deprivation is a prelude to these events. Our present belief is that any disturbance which brings about hormone deprivation in the last trimester of pregnancy results thereby in a metabolic change in the uteroplacental area with the formation of a substance to which may be attributed the final manifestations of toxemia.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—May I ask the essayist when the females were sacrificed? If the lesions described were present before the thirty-second day of pregnancy, they might quite conceivably be attributed to hormonal influences. If, on the other hand, they occurred in association with artificial prolongation of pregnancy in animals sacrificed, let us say, on the thirty-fifth or thirty-sixth day, one cannot help but think of overdistention of the uterus as an etiologic factor. It would seem important that this question be answered.

DR. FRED L. ADAIR, Chicago, Ill.—A number of years ago Dr. Ruth Watts and I undertook, in our Clinic, some investigations in regard to the effect of growth hormone upon gestation. We were more particularly concerned with the possible relationship between the administration of the growth hormone and the development of the fetus. In connection with this work on the rat, certain accidental findings were encountered which fit in with Dr. Snyder's thesis this morning. I would like

briefly to present some of these findings indicating that a similar condition develops in a different species.

Anterior pituitary extracts often prolong gestation in the rat. This is at times accompanied by separation of the placenta and death of the fetus in utero, prolongation of parturition, and failure of the birth mechanism. Unfortunately, we did not realize at that time the possible connections of these findings with the toxemias of pregnancy, and other organs were not studied.

Six rats delivered at twenty-three to twenty-six days instead of twenty-two days. These rats received growth hormone beginning from the sixth to the tenth day of pregnancy and continued to delivery. Thirty-eight of the 42 young were stillborn, macerated, or being resorbed. Vaginal bleeding preceded delivery and labor was often prolonged over several days. The normal birth mechanism seemed to fail completely.

One rat injected from the twelfth day on died on the twenty-sixth day. The uterus was found filled with blood with the placentas detached and surrounded by large clots of blood. The young were black and partially resorbed.

Six rats were injected beginning with the tenth day and autopsied from the twenty-fourth to the twenty-seventh day of pregnancy. On the twenty-fourth day the young were still alive if the placentas were attached. The placentas were usually partially or entirely detached, however, and the young were then dead, often for a long period of time, and were black and being resorbed. Sometimes the placentas adhered to the uterine wall but were easily detached so that two or more placentas could be removed at one time.

Cesarean section was performed on 2 rats on the twenty-fourth and twenty-six days of pregnancy. Both had received hormone from the tenth day. The rat on the twenty-fourth day had a grossly normal litter but the young were sluggish and there were clots around the placentas. The rat autopsied on the twenty-sixth day had partially delivered two dead fetuses previously but the rest of the litter of eight were dead and being resorbed.

Four rats were autopsied at term. These rats had received hormone from the twelfth day. The young were all normal and living with the exception of 3 of one litter which were not found and whose placentas were abnormal or reduced to "tarry" masses. The remaining placentas in this rat and two other rats were firmly attached, but some of the placentas of the fourth rat had large blood clots.

EXTRACT NO.	DELIVERY 22-23 DAY	DELIVERY LATER THAN 23 DAY	AUTOPSY 22 DAY	NO. PREG.	TOTAL RATS	TOTAL PREG.	TOTAL PROLONGED PREG.
Phyone 32	4	11	0	2	17	15	11 (73%)
Misc.	11	11	3	1	26	22+3	11 (50%)
Phyone 34	7	1	0	0	8	8	1 (12.5%)
Special Ext.*	18	5	0	0	23	23	5 (23%)
	40	28			74	58+3	28 (48%)

*Fractionations of these extracts show that the factor prolonging pregnancy is a contaminant of the growth hormone and is more soluble at pH-7 than is the growth hormone.

DR. SNYDER (closing).—With regard to the state of the fetus, the first specimen I took is a typical one. The fetus was alive and the animals were killed because of external bleeding. Of course, the study has been amplified a great deal. We have had animals that have retained their fetuses for several hundred days but that is not a part of this discussion.

This is certainly a complicated problem and I have tried to confine the description to anatomic terms based on the rabbit. Of course, the hormonal relationships in the rabbit are a problem in themselves.

SELECTIVE HYSTERECTOMY FOR NONMALIGNANT UTERINE DISEASE*

EDWARD G. WATERS, M.D., F.A.C.S., JERSEY CITY, N. J.

THE term "selective hysterectomy" implies that diverse operative procedures are available for adequately treating nonmalignant uterine disease. The qualifying adjective infers that limitation of hysterectomy to but one operative technique is unsound.

A diseased uterus may be removed by total vaginal hysterectomy, supravaginal hysterectomy, or total abdominal hysterectomy. The subject matter here presented is based upon relevant literature and personal experiences for the past fifteen years and represents an inquiry into the factors which determine choice of operation for the condition encountered.

With few exceptions as to operators and indications, vaginal hysterectomy is reserved for patients with moderate-sized tumors and large vaginal passages, or as an associated procedure accompanying correction of prolapse. Resorting to a Schuchardt incision to secure room for vaginal hysterectomy is rarely justified. It is a bloody, easily infected incision which heals poorly and with much granulation tissue. One must carefully assess the presumed value of a contemplated vaginal operation against the frequent perils of this incision. It has been my experience that if one excludes cases with procidentia or ample parous passages, abdominal hysterectomy is safer and accompanied by fewer complications. Since vaginal hysterectomy is performed largely on selected and pathologically uncomplicated cases, the admittedly lower mortality and morbidity rates are anticipated. It is seldom a shocking operation and the postoperative course is usually excellent. To avoid operative risk the patient must have a freely mobile uterus, and the cervix must descend with traction to the vulva. Even with palpably mobile structures, previous operations make the pelvic status uncertain until the operation is well advanced, and the vaginal route should be avoided unless the exact nature of such pelvic surgery is known. When a tumor requires morcellation to reduce it, unexpected dangers may arise. I know of two nephrectomies necessitated by vaginal removal of large tumors by morcellation.

With suitable local conditions and indications vaginal hysterectomy is the best operation for totally removing the uterus, especially in old or obese women or in poor surgical risks. When the vagina is small, the uterus fixed or adherent, and the uterine tumor large, the surgeon's grief may know no bounds should he attempt it, and through such a

*Read, by invitation, at the Sixty-Seventh Annual Meeting of the American Gynecological Society, Skytop Lodge, Pa., June 15 to 17, 1942.

vagina a totally unreasonable risk is assumed. Reoperation for recurrent cystocele, intestinal obstruction, or enterocele are not rare following operation by competent surgeons.

With these limitations in mind, we may say that vaginal hysterectomy is a safe procedure well within the compass of the competent gynecologist for the conditions and indications outlined. Beyond this it becomes a hobby, whether expertly performed or inexpertly inflicted.

In the author's group of hysterectomies, there were 83 cases of vaginal hysterectomy. This does not include two which were attempted but thwarted by old abdominal fixation operations, and successfully completed abdominally. Two developed enteroceles which were subsequently corrected. There were 6 recurrences of cystocele. The bladder twice was inadvertently opened, but sutured in layers and the vaginal hysterectomy proceeded with. No fistulas resulted. There were no immediate operative deaths. One 68-year-old patient died six weeks postoperatively at home from some undetermined abdominal condition. Three patients showed evidence of intestinal obstruction. One was from fecal impaction due to improper preoperative preparation. Only one required operation. A loop of ileum was kinked and adherent in the culdesac and release of the obstructed bowel sufficed as a cure.

The trend toward total hysterectomy for all non-malignant uterine disease prompts an unbiased inquiry into the reasonability as well as the results of the methods commonly chosen.

The controversy of complete versus supravaginal hysterectomy would seem to indicate a move from a relatively simple operation to one immediately awesome and threatening in its application. For the majority of patients either operation may be done with safety and facility by any competent operator. What then are the further steps which one takes when the contemplated supravaginal operation is converted into a total hysterectomy? Briefly, these:

The bladder is separated not only from the cervix but also from the anterior vaginal vault, by dividing the uterovesical fascia. The uterine vessels are well exposed, ligated and divided about 1 cm. lateral to the internal os, and the stumps pushed out and away from the uterus, carrying the ureters out with the fascia and away from danger. The thickened endopelvic fascia lateral to the cervix, the ligament of Mackenrodt, is clamped, cut and sutured, thus freeing the cervix laterally. The uterosacral ligaments are tied and cut close to the internal os and the peritoneum divided between them. The vagina is opened anterior to the cervix, or a posterior vaginal opening may be chosen, and the vagina circumcised close to the cervix. The vaginal mucous membrane and fascia is then closed, the vagina supported by re-attaching the broad, round and uterosacral ligaments and the operative area reperitonized.

The sole advantage of a complete hysterectomy lies in the removal of the cervix. The operation combines therapy for existing cervical

disease with prophylaxis against future infection or cancerous change. The "selling point" rests upon prevention of posthysterectomy stump carcinoma and cervicitis. Supravaginal hysterectomy possesses certain compensating advantages. It is done more rapidly and with little blood loss. There is less danger to the urinary structures and no drying or constriction of the vagina. Of first importance is the maintenance of adequate vaginal support by retaining the normal cervical fascial attachments, the keystone of the vaginal vault.

Published opinion on abdominal hysterectomy for fifteen years may be divided with some accuracy into (1) those favoring supravaginal hysterectomy, and (2) those relying mainly upon total hysterectomy.

Hochman, in an analysis of 1,114 supravaginal operations at the Woman's Hospital in New York, found three cases of stump cancer. Preoperative treatment of the cervix by conization or carbolization helped to prevent subsequent endocervicitis and lessened the development of stump cancer. While the occurrence of stump cancer did not warrant panhysterectomy with its greater mortality, every cervix should be inspected and definitely diseased cervical tissues should be thoroughly removed. Kostmayer concluded "since eventual mortality is the same for total hysterectomy, and supravaginal hysterectomy plus carcinoma in the remaining cervix, I prefer the deaths to come from the latter and give the years of intervening life to the patient. Leave the cervix, watch it, and treat it." Healy and Arneson studied 67 patients with stump carcinoma, and did not believe the low incidence justified the higher mortality of total hysterectomy. Seley, quoted by Sackett, found the mortality in 3,088 hysterectomies to be 2.3 per cent for the supravaginal and 3.98 per cent for the total operation, although Farrar, from the same clinic, favored total hysterectomy. From his own statistics, Joe Meigs believed cancer of the retained cervix as not more likely after subtotal hysterectomy, but half as likely, as in women as a whole. He advocated the total operation only where cervical repair or amputation was difficult and cauterization out of the question. He considers the cervices of nullipara or patients with fibroids as especially bad, since a larger percentage of these developed stump cancer. Phaneuf and Belson favor the supravaginal operation, although stressing the need for selecting the operation to the condition of the patient and her age, and Bland in discussion agrees. Harris, reporting 739 cases, found the incidence of the total operation increasing, and carrying a persistently higher mortality than the supravaginal under similar elective conditions. Dannreuther generally favors supravaginal hysterectomy.

As against these selected views favoring supravaginal hysterectomy, there is formidable disagreement.

Baldwin (in discussion of Phaneuf) advises pan-hysterectomy "always," since he believes the cervix is useless and he records more than 40 cases of stump carcinoma after supravaginal hysterectomy. Gellhorn and Spain and Waldeyer advise routine complete hysterectomy and Von Graff, after collecting a large number of cases of stump carcinoma, is in agreement. Smith of Danforth's Clinic, in an analysis of 1,200 hysterectomies, had a lower mortality for the total operation, although

Masson, urging careful selection of cases, definitely believes that the total operation carries a higher mortality. In Faulkner's report on 1,544 cases, the mortality varied little in the different types of operations. Goodall has shifted his preference to the total operation, with no regrets. On the other hand, Murphy reported ureteral and bladder injuries ten times more frequent after complete hysterectomy than after supravaginal operations, where all cases were operated upon by well-trained men in a good hospital. Counsellor disbelieves the need for unfavorable sequelae to total hysterectomy, which he favors, and has described a technique to overcome them. Pearse performs total hysterectomy almost as a routine and Weir does a supravaginal hysterectomy only when complications are so extensive that panhysterectomy cannot be done with safety.

What conclusions may be drawn from such varied and conflicting opinions as to the relative safety and facility of total and supravaginal hysterectomy?

It would seem that in average and often in expert hands, the total operation carries greater morbidity and mortality for *comparable* cases, since it involves a more difficult and dangerous technique. An appeal from this statement may be found in many of the foregoing series which indicate that the mortality and morbidity rates of the complete and supravaginal operations do not materially differ. Reappraisal of most of these data will show the supravaginal procedure to have been followed when pelvic complicating factors made the complete operation either impossible or unreasonably hazardous. Comparing data of complete operations done in good risk cases with clean pelves, with supravaginal operations performed upon patients with huge tumors, extensive pelvic adhesions, coexisting endometriosis or residual pelvic inflammatory disease, is unconvincing statistical deception. It would seem better to admit the necessity and preference in given cases for the suitable and safe operation, which might be either.

Since the outstanding and apparently only accomplishment of total hysterectomy not possessed by the supravaginal operation, is the removal of a cervix which may postoperatively become the seat of cancer or infection, or is a distorted result of parturition, let us first consider recorded opinion on stump cancer.

As already noted, there is considerable difference of opinion regarding the *frequency* of stump cancer. Fahndrich collected 395 cases with an incidence of about 0.4 per cent. Von Graff's figures would indicate that 4 per cent of all cervical cancers are of the retained stump. Fricke and Bowing reported 57 stump carcinomas in 1676 cervical cancers or 3.4 per cent. Pearse's 34 cases of stump cancer represent 5.6 per cent of all cervical cancer seen. Healy and Arneson, Hann, Benda, and Hochman question a high cancer incidence in the retained stump. And when it does occur, there are varying opinions as to its relative danger. It was formerly believed that it was generally not far from hopeless when discovered, but Behney has recorded 67 cases with results of treatment no worse than in cervical cancer in general, and Ward agrees that results generally are better than in cervical cancer where no opera-

tion had been done. This he ascribes to the diminished cervical circulation and interference with lymphatic drainage.

For the unbiased, the dissimilarity in published experience reveals the status of stump carcinoma as highly unsettled. Whether the death incidence from stump carcinoma after supravaginal hysterectomy balances or overcomes the more unfavorable operative figures for the total operation is debatable. While cancer in a clean, retained cervix is a rarity, it nevertheless is a positive postoperative danger, entirely irrespective of the merits of controversial opinion as to its frequency.

Infection of the retained cervix is a more frequent sequel, always mentioned and immediately forgotten. It may cause no end of discomfort until treated and as a constant possibility it should receive due attention at operation.

Since cancer in the retained stump does occur, and since cervical infection develops on occasion when a total hysterectomy is either impossible or inadvisable, various methods have evolved for managing the cervix prior to performing supravaginal hysterectomy. The purpose of these several techniques is the removal or destruction of the cervical mucosa, by carbolization, by actual cautery, or by electric conization, as recommended by Hochman, Donay, Bland, Sutton, Kelly, Polak and others.

Cashman and Frank cauterized 82 per cent of cervices prior to supravaginal hysterectomy in 1,464 cases, with a gross mortality of 1.91 per cent. Such a procedure may eliminate postoperative cervicitis, but can hardly prevent stump cancer where, as noted by Von Graff, over 80 per cent of these develop from the squamous cells of the vaginal portion. Miller and Todd in 1938 described a technique for cervical conization suitable for use prior to supravaginal hysterectomy and recorded favorable results in 899 cases. This experience was in accord with that of Stadiem who recommended it routinely with supravaginal hysterectomy and always where panhysterectomy might be hazardous.

For the past twelve years it has been my custom to do an electrocervicectomy prior to proposed or probable supravaginal hysterectomy. The technique consists in conization using a Bovie or similar current with a modified Hyam's loop, deep enough to remove all of the gland-bearing tissue of the endocervix. A wire loop then excises a large part of the portio vaginalis.

While epidermoid carcinoma arises characteristically at or near the margin of the external os, it may arise somewhat further from this margin, although this is uncommon in the recorded experience of those few men who have seen considerable numbers of early cervical cancers. It may possibly arise from the sites of squamous cell metaplasia seen in endocervical glands. An electrocervicectomy will remove all of these potential cancer or infection sites quickly, easily and safely.

In 18 of the cases where electrocervicectomy preceded total abdominal hysterectomy, postoperative sections made through the uterus

and coned area of the cervix showed the effectiveness of this technique in eliminating the danger zones.

It is not necessary to stress the value of a danger-free cervix as a support for the vaginal vault in maintaining vaginal depth, and in closing the opening in the pelvic fascial diaphragm. Any function the fibromuscular, mucosa-free cervical stump may possess in retarding atrophy of retained ovaries is admittedly dubious, but still theoretically possible.

PERSONAL SELECTION OF OPERATION

In 388 hysterectomies* reviewed there were 83 vaginal hysterectomies, with results as previously noted. Of the other 305 cases, 208 were supravaginal hysterectomies, of which 94 had associated vaginal plastic operations. One hundred fourteen or 55 per cent of these supravaginal hysterectomies were preceded by electrocervicectomy. The morbidity in the 208 cases was 16.2 per cent. There were 4 deaths with a mortality of 1.9 per cent. One death followed forty-eight hours after injudicious electrocervicectomy for infected cervical polyp prior to supravaginal hysterectomy. One patient died from transfusion reaction 6 hours postoperatively. One died from peritonitis and one from pulmonary embolism. Ninety-seven total hysterectomies were performed.

In three cases, conditions made the immediate removal of the diseased cervix unduly hazardous. The uterus was removed supravaginally, and then the cervical stump grasped with a crossed tenaculum inserted into the canal. This was used to lift and manipulate the cervix while its isolation and excision was completed. There were no deaths in the total hysterectomy cases. The morbidity was 20.4 per cent. No ureters are known to have been injured. One patient developed intestinal obstruction six weeks postoperatively, successfully corrected by operation. Three cases developed marked thrombophlebitis of the lower extremities.

The intent of this presentation is not to array overwhelming statistical minutia. It represents a smaller, personally operated-upon and cared-for group. Therefore, while admitting numerical limitations and with no attempt to rival many excellent and exhaustive analyses already on record, it is felt that this personal study constitutes a basis for discerning analysis sufficient to justify the views expressed concerning operation selection.

CONCLUSIONS

Hysterectomy for nonmalignant uterine disease should be a selective operation, with the choice resting upon condition of patient and pathology, for the best immediate and ultimate outcome to the patient.

The vaginal route is preferred for patients with ample vagina, or with descent at least equivalent to a second-degree prolapse, and only moderate uterine enlargement. It is the choice where hysterectomy is indicated in the old, the obese, the debilitated.

When abdominal hysterectomy is planned, the total operation is the *preferred* technique unless the patient has a very deep pelvis,

*Personally operated private and service cases at Christ and Fairmount Hospitals.

a short vagina or the size of the pelvic tumor or associated pelvic pathology introduce risks out of proportion to the dangers inherent in a residual cervical stump. It is always preferable, although not always possible, to remove a badly distorted cervix with the uterus, rather than perform a plastic operation upon it.

Supravaginal hysterectomy is the *safer* technique for removing the uterus where pelvic conditions make the operation slow, sanguineous or dangerous. The hazards of posthysterectomy cervical stump cancer or infection can be removed effectively by combining radical cervical conization, or electrocerviceectomy with supravaginal hysterectomy. This vaginal-abdominal approximation of total hysterectomy, leaving a fibromuscular cuff of cervix, combines the advantages of both total and supravaginal operations and possesses the disadvantages of neither. It is recommended as a safer procedure in average hands than a total hysterectomy for all cases, and as a safer procedure even in expert hands, than total hysterectomy in "bad risk pelves."

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DISCUSSION

DR. EDWARD H. RICHARDSON, BALTIMORE, MD.—This paper of Dr. Waters brings before the Society very properly an annual topic of discussion. With most of his thesis I am in complete agreement. The title very properly indicates that there is no established procedure for removing the uterus that is equally applicable to all cases.

I would like to recommend in suitable cases substitution for vaginal hysterectomy the operation which I published about five years ago under the title of "composite operation," which owes its existence to the fact that I have been repeatedly confronted by patients upon whom total vaginal hysterectomy had been performed by other surgeons and later developed varying degrees of vaginal prolapse, enterocele, cystocele, et cetera. I endeavored to discover what factors in the several operative procedures now widely employed were responsible for these recurrences and failures, and the composite operation was constructed upon the foundations of that analysis. I simply eliminated from the established procedures those factors which I considered responsible for the failures, and then combined those steps which time had proved to be dependable.

Our experience for the past five years with this operation has convinced me of the superiority of it over total vaginal hysterectomy as a reconstructive procedure for many combinations of vaginal hernias. Certainly it does not seem reasonable routinely to employ total vaginal hysterectomy in this type of case if we focus our attention for a moment upon the importance of the upper pelvic floor as the chief support of the pelvic viscera. I conceive of this anatomic structure as composed simply of two suspension bridges constructed at right angles to each other, the cardinal ligaments constituting the transverse bridge, while the pubocervical fascia in front together with the uterosacral ligaments posteriorly are the chief components of the anteroposterior bridge. Both of these bridges owe their mechanical efficiency as supporting structures mainly to the fact that they are firmly anchored into a small segment of the cervix at the level of and adjacent to the internal os. In a total vaginal hysterectomy the first thing you do is to crush these structures with a clamp, then divide them. You then further impair their circulation by suturing them together. The result is a number of recurrent vaginal hernias. The composite operation by contrast safeguards the vital keystone, that little upper segment of the cervix together with its fascial supports, but removes the two portions of the uterus in which carcinoma occurs; namely, the corpus above the level of the internal os and the diseased part of the cervix below the cardinal ligaments. This plan also greatly diminishes the danger of damage to the ureters. By preserving the upper pelvic floor intact adequate support for correction of associated types of hernia is provided in accordance with sound surgical principles. Our results are certainly convincing so far as the ultimate outcome of these cases is concerned. The operation does require patience and accurate knowledge of the anatomy. Nobody but an experienced operator should undertake it. It is more time consuming too, but the end results are far superior to the other types of operation now in general use for the treatment of uterine prolapse and associated vaginal hernias.

Concerning the controversy of total versus subtotal abdominal hysterectomy, I do not see why there should be any difference of opinion about the desirability of removing every diseased cervix. Unfortunately, often there is some contraindication for so doing, and the operator is compelled to perform a subtotal operation and knowingly to leave a diseased cervix. On the other hand I have been unable, in following the literature of the last few years, to find a single convincing reason that would justify the routine removal of normal cervices.

I think the arguments that have been built up on the incidence of stump cancer, for example, are totally fallacious. I know of no work that has been done to

show the actual incidence of stump cancer in normal cervices that were left behind. Surely there is every reason to believe that the vast majority of stump cancers have occurred in cases where subtotal operations were done because the complicated pathology encountered or the patient's condition, or the limited experience and skill of the operator, did not warrant the more radical procedure, and a diseased cervix was left untreated. In my entire experience I have seen only one instance of stump cancer where I left a normal cervix. I do not believe, therefore, that routine removal of the normal uterine cervix should be done. Total abdominal hysterectomy is certainly a more dangerous and more hazardous operation from the standpoint of morbidity as well as of mortality, as will immediately become evident if analysis is made of equally severe grades of pathology treated by the two methods. Otherwise, how can you explain, for example, the paper presented today on the incidence of urinary tract fistulas following this operation?

I believe it is a very unfortunate thing that this Society still remains divided in opinion on this matter and I think it is a dangerous teaching to go out into the country that surgeons who are less competent than this group of men should routinely do total abdominal hysterectomy even though the cervix is normal. I am emphatically opposed to this teaching and practice.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—I agree with the author of this paper that no routine operation should be performed in all cases, but the operation should be adapted to the case at hand. A trained gynecologist should be able to do a complete abdominal or a vaginal hysterectomy with as much ease and familiarity as a supravaginal hysterectomy. A supravaginal hysterectomy should not be the choice of an operator because he cannot do a vaginal hysterectomy or complete abdominal hysterectomy. The advantage of a vaginal hysterectomy is apparent, when I say that the number of vaginal hysterectomies, since we began the use of ethylene, now totals, 1,056 completed cases with only 3 deaths.

One objection to a vaginal hysterectomy which is often mentioned is shortening of the vagina. If one performs vaginal hysterectomies only for prolapse, I can see why that idea arises, for in such cases, the vagina is always shortened because the caliber of the tube has been increased. When the vagina is of normal length to begin with, no shortening occurs. If the vagina is incised at the same place, I cannot see why removing the uterus from below will shorten the vagina more than if it is removed from above. Logically the vagina should be shortest after a supravaginal hysterectomy because the retained cervix detracts from the length of the vagina.

If I am not going to take the cervix out I leave it strictly alone. I do not believe it should be burned or excoriated, because you cannot do either of these things and not have it invaded by the flora of the vagina and thus have an infected cervix. If you add cauterization of the cervix to a supravaginal hysterectomy, I think you are courting serious trouble.

DR. JOE V. MEIGS, BOSTON, MASS. (By invitation).—Three of my patients have had cancer of the cervical stump following supravaginal hysterectomy and I had to explain to them that at operation I had left the cervix in and that I did not take it out because it was a difficult procedure. Since I have been at the Pondville Hospital, out of 1,200 cases of cancer of the cervix seen there we have had 100 cancers of the cervical stump. Many of these cancers were doubtless present at the time of their supravaginal hysterectomy and some developed cancer many years afterward. Because of 3 cases occurring in my own patients and of seeing 100 cases at the State Hospital, I advocate removal of the cervix wherever possible.

About 10 per cent of our cases of cancer of the cervix occurred in nulliparas. I do not believe one can tell when a cervix may develop cancer. I feel sure that from now on whenever possible I will do a total hysterectomy until I am taught differently by my own experience.

DR. GEORGE GRAY WARD, NEW YORK, N. Y.—I would like to endorse what Dr. Meigs has just said as I heartily agree with his point of view. In my clinic at the Woman's Hospital in 1940 we found that about 7 per cent (6.9 per cent) of the 879 cases of cervical cancer had cancer of the stump. We also have had nulliparas among that number. I believe that the entire uterus should be removed provided it will not be a matter of undue risk to the patient. The total operation is preferable because of the evident higher incidence of stump cancer than was formerly thought to occur, and of the frequent association of cancer with fibroids. Conization or cauterization of the cervical canal is no safeguard as 80 per cent of cancers of the cervix originate on the portio vaginalis.

DR. WILLIAM P. HEALY, NEW YORK, N. Y.—I have had in my private practice a large group of patients returning to me for annual examinations. In all those years I have had only two instances where cancer has developed in the cervix remaining after a supravaginal hysterectomy done by me.

One of these occurred in a woman who had had a supracervical hysterectomy in her early forties. Except for the uterine myomas, she had been in excellent health, had never conceived, and had a perfectly normal cervix. She later came to me with vaginal spotting. The cervical lesion was less than 1 cm. in size and noninfiltrating, but coincidentally she had a large pulmonary carcinoma. We assumed the cancer in the lung developed first but that we were dealing with an instance of double primary carcinoma.

At the Memorial Hospital Dr. Arneson and I went over about 1,000 cases and we found that only 2 per cent of our cases were bona fide stump carcinomas, in which epidermoid carcinoma had developed in the cervix.

I feel therefore as Dr. Richardson does, that for us to recommend panhysterectomy just because we are removing the corpus when the patient has a normal clean unlacerated and uninfected cervix, is carrying the argument further than we really need to do, especially if you are following up these patients and looking after their general health.

DR CURTIS F. BURNAM, BALTIMORE, MD.—Dr. Howard Jones of the Kelly Clinic has recently reviewed 900 consecutive cases of carcinoma of the cervix. Excluding those sent for prophylactic radiation after panhysterectomy and those treated by radium elsewhere before coming to us, there remained approximately 700 cases. Among these 700 cases, 51 were carcinomas of the stump or 7 per cent. Of these 51 cases, however, 16 had developed within two years of the supravaginal hysterectomy. It seems only fair therefore to assume that these cancers may have been present at the time of the operation. This leaves us 35 cases or about 5 per cent.

I realize that one cannot calculate the occurrence of cancer of the cervix after supravaginal hysterectomy from such material. The only conclusive way for this to be done would be to go over a very large series of supravaginal hysterectomies. It seems to me this could be easily done if a dozen of the big clinics would cooperate to do this work for us.

It is evident that before doing any gynecologic operation, much less a hysterectomy, that a thorough examination of the patient should be made under gas with biopsy from the cervix, curettage and all other methods of diagnosis utilized. To be able simply to look at a cervix and tell positively whether it is precancerous or not is beyond my powers of diagnosis.

DR. SAMUEL A. COSGROVE, JERSEY CITY, N. J.—I believe that our thinking would be straighter if we expressed ourselves in the same way. Dr. Meigs and several other speakers have said that they found cancer of the cervical stump in 7 or 8 per cent of the cases observed after supravaginal hysterectomy. Those who approached the subject from the other end and surveyed their hysterectomies, found 2 per cent or less of stump cancer. We cannot come to a common understanding

unless we get our facts lined up on the same basis. Those who have recorded series of cases of cancers of the cervix say nothing about the incidence of hysterectomy in the general population of which 8 per cent of carcinoma of the cervix represents a cross section. I think this whole problem might better be turned over to statisticians rather than gynecologists.

DR. E. H. RICHARDSON, BALTIMORE, MD.—I cannot see that the incidence even of 7 per cent of stump cancers reported from some clinics has any bearing on the position that I have taken. This position is, that when a cervix is diseased it should either be removed with the uterus or at a second operation, and when normal it should not be removed. Is there any basis whatsoever upon which you can pick out of the stump cancers those cases that developed in normal cervices? Is it not obviously absurd to assume that all of these cervices were normal when the subtotal operation was done? Certainly it is far more rational to assume that they were left because of extensive pelvic disease that precluded judicious use of total hysterectomy. If so, one must conclude that these cervices also were diseased and were left untreated later to supply the 7 per cent incidence of stump cancers now being fallaciously put forward in advocacy of routine removal of normal cervices.

DR. WATERS (closing).—I will answer one question specifically, as to when electrocervicectomy was used. It was done immediately before the operation if the cervix was not acutely infected. It preceded operation when a total hysterectomy seemed impossible because of some existing condition. Infected cervices were treated weeks in advance of operation.

As to stump cancer, I found the differences of opinion essentially the same fifteen years ago as expressed here. Even with total excision of the uterus, one will occasionally find later a cancer of the vault, so that you still cannot completely escape it.

With deep regret we announce the death of Dr. Charles Virgil Mosby, Chairman of the Board of The C. V. Mosby Company, St. Louis, on Monday, November 9, 1942.

His vision and courage will continue as an inspiration throughout the future of the company that he founded.

Items

American Board of Obstetrics and Gynecology

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 13, 1943, at 2:00 P.M.

Arrangements will be made so far as possible for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates for the February 13, 1943, Part I examination, who are entering military service, or who are now in service and may be assigned to foreign duty, may submit their case records in advance of the above date, by forwarding the records to the Office of the Board Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon-General (U. S. Army) has issued instructions that men in service, eligible for Board examination, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

All candidates will be required to take both the Part I examination, and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.

The Part II examination will be held at Pittsburgh, Pennsylvania, from May 19-25, 1943. Notice of the exact time and place of the examinations will be sent all candidates well in advance of the examination date. Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations applying to civilian candidates.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

American College of Surgeons Cancels Clinical Congress

The annual clinical Congress of the American College of Surgeons which was scheduled to be held in Cleveland, Nov. 17-20, 1942, was canceled by the Board of Regents of the College at a meeting held in Chicago, Wednesday morning, October 14.

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